Title
Small molecule inhibitors of epithelial-mesenchymal transition for the treatment of cancer and fibrosis

Journal
Medicinal Research Reviews, 40(1)

ISSN
0198-6325

Authors
Feng, Ya-Long
Chen, Dan-Qian
Vaziri, Nosratola D
et al.

Publication Date
2020

DOI
10.1002/med.21596

Peer reviewed

Received: 18 January 2019 | Revised: 20 March 2019 | Accepted: 26 April 2019

DOI: 10.1002/med.21596

WILEY

REVIEW ARTICLE

Small molecule inhibitors of epithelial-mesenchymal transition for the treatment of cancer and fibrosis

Ya-Long Feng[1] | Dan-Qian Chen[1] | Nosratola D. Vaziri[2] | Yan Guo[1,3] | Ying-Yong Zhao[1]

[1]School of Pharmacy, Faculty of Life Science & Medicine, Northwest University, Xi'an, Shaanxi, China

[2]Department of Medicine, University of California Irvine, Irvine, California

[3]Department of Internal Medicine, University of New Mexico, Albuquerque, New Mexico

Correspondence
Ying-Yong Zhao, Professor, PhD, MD, Faculty of Life Science & Medicine, Northwest University, No. 229 Taibai North Road, Xi'an, 710069 Shaanxi, China.
Email: zyy@nwu.edu.cn; zhaoyybr@163.com

Funding information
National Natural Science Foundation of China, Grant/Award Numbers: 81603271, 81872985, 81673578

Abstract

Tissue fibrosis and cancer both lead to high morbidity and mortality worldwide; thus, effective therapeutic strategies are urgently needed. Because drug resistance has been widely reported in fibrotic tissue and cancer, developing a strategy to discover novel targets for targeted drug intervention is necessary for the effective treatment of fibrosis and cancer. Although many factors lead to fibrosis and cancer, pathophysiological analysis has demonstrated that tissue fibrosis and cancer share a common process of epithelial-mesenchymal transition (EMT). EMT is associated with many mediators, including transcription factors (Snail, zinc-finger E-box-binding protein and signal transducer and activator of transcription 3), signaling pathways (transforming growth factor-β1, RAC-α serine/threonine-protein kinase, Wnt, nuclear factor-kappa B, peroxisome proliferator-activated receptor, Notch, and RAS), RNA-binding proteins (ESRP1 and ESRP2) and microRNAs. Therefore, drugs targeting EMT may be a promising therapy against both fibrosis and tumors. A large number of compounds that are synthesized or derived from natural products and their derivatives suppress the EMT by targeting these mediators in fibrosis and cancer. By targeting EMT, these compounds exhibited anticancer effects in multiple cancer types, and some of them also showed antifibrotic effects. Therefore,

drugs targeting EMT not only have both antifibrotic and anticancer effects but also exert effective therapeutic effects on multiorgan fibrosis and cancer, which provides effective therapy against fibrosis and cancer. Taken together, the results highlighted in this review provide new concepts for discovering new antifibrotic and antitumor drugs.

KEYWORDS
cancer, epithelial-mesenchymal transition, fibrosis, natural product, small molecule, transcription factor, tumor

1 | INTRODUCTION

Tissue fibrosis and cancer are two major causes of high human morbidity and mortality worldwide. Although there are multiple therapies for cancer, including chemotherapy, oncologic surgery, and radiation therapy, an effective therapeutic strategy is needed.[1] Among these therapeutic strategies, chemotherapy is the main tool for curing various cancers. The therapeutic resistance of anticancer drugs, such as 5-fluorouracil, gemcitabine, gefitinib, and trastuzumab, has been widely observed in the clinic.[2] However, due to the lack of effective therapeutic drugs, tissue fibrosis still threatens human health. Although some drugs exhibit antifibrotic effects, including angiotensin-converting enzyme inhibitors, aldosterone inhibitors, statins, angiotensin II type 1 receptor blockers, endothelin receptors, β-blockers, acetylsalicylic acid, and matrix metalloproteinase (MMP) inhibitors, none of them are specifically designed to target fibrosis, and the related side effects limit their clinical use for treating fibrosis.[3-6] Thus, antifibrotic and anticancer treatments are extremely urgent, and new therapeutic drugs should be designed based on specific targets that contribute to the progression of fibrosis and tumors.

Epithelial-mesenchymal transition (EMT) is a reversible terminal differentiation process in which epithelial cells shed their properties and acquire a more mesenchymal phenotype.[7] EMT is a fundamental process widely involved in the development and the progression of various diseases, and there are mainly three types of EMT[8] (Figure 1). Type I EMT is involved in embryonic development and organ formation. Type II EMT is critical for wound healing and fibrosis. Type III EMT contributes to the progression and metastasis of tumors.[9] Extensive studies revealed that EMT profoundly contributed to the production of myofibroblasts, which are the major cells producing massive amounts of collagen that leads to the deposition of collagen in the development of fibrosis.[10] In addition, EMT confers increased motility and invasiveness in epithelial-derived tumor cells and promotes tumor metastasis. Therefore, fibrosis and tumors share the common process of EMT, and drugs that specifically target EMT may exhibit both antifibrosis and antitumor effects, which will provide an effective strategy against fibrosis and tumors.

Small molecules have a long history of acting as drugs for the treatment of hypertension, infections, heart failure, diabetes, asthma, rhinitis, and tumors and comprise approximately 75% of the anticancer drugs approved by the FDA from 1981 to 2014.[11] Recently, many small molecules target EMT and exhibit good therapeutic effects on retarding progressive tissue fibrosis and cancer in experimental conditions.[12-14] In addition, it is worth noting that many small molecules, such as tivantinib, trametinib, linsitinib, nintedanib, and binimetinib, are in ongoing clinical trials for the treatment of tumors.[2] These cases show promising prospects for treating fibrosis and cancer, which encourages researchers to find effective small molecule drugs for treating fibrosis and cancer.

In this review, we describe some important transcription factors, signaling pathways, RNA-binding proteins and microRNAs (miRNAs) and several novel regulators that contribute to EMT and further present some small

molecules that exhibit therapeutic effects against EMT. Targeting these mediators with these compounds may be a promising therapeutic strategy to treat fibrosis and cancer.

2 | SMALL MOLECULES AGAINST EMT

Several excellent reviews have discussed the mechanisms of EMT well.[15] Briefly, histological and pathological analyses show that epithelial cells are present in single cell layers or multilayers and show apical-basal polarity. Epithelial cells not only interact with the basement membrane with integrins but also communicate with each other via specialized intercellular junctions, including desmosomes, subapical tight junctions, adherens junctions and scattered gap junctions. These interactions help maintain epithelium integrity and function. However, some stimuli drive EMT in pathological conditions. During the process of EMT, epithelial cell-cell junctions are dissolved, and the epithelial cells lose their apical-basal polarity and acquire front-rear polarity. In addition, the cytoskeletal architecture is reorganized, and E-cadherin expression is replaced by N-cadherin expression, which enhances cell motility and invasiveness. In fibrosis, mesenchymal-like cells transform into myofibroblasts, which can be activated to produce excessive collagen, and in tumors, these mesenchymal-like cells migrate along with the circulatory system to a secondary location where they form a secondary tumor via mesenchymal-epithelial transition (MET).[16] It is worth noting that tissue fibrosis and tumors share the common process of EMT, which suggests that targeting EMT may be an effective strategy to treat both fibrosis and tumors (Figure 1). EMT is regulated by various mediators such as transcription factors, signaling pathways, RNA-binding proteins, and miRNAs. In addition, there are many small molecules that exhibit effective therapeutic effects on tissue fibrosis and tumors by suppressing EMT via targeting these mediators.

2.1 | Inhibition of transcription factors by small molecules

Transcription factors such as Snail, Twist, zinc-finger E-box-binding homeobox (ZEB) and signal transducer and activator of transcription 3 (STAT3) are activated early and play central roles in the EMT. They not only repress the epithelial phenotype but also activate the mesenchymal phenotype individually or by cooperating with other transcription factors. Thus, inhibiting the activation of transcription factors may be an effective way to block EMT to treat fibrosis and tumors. Indeed, many compounds significantly intervene in fibrosis and tumors by suppressing the activation of transcription factors.

2.1.1 | Snail transcription factors

Snail is a zinc-finger transcriptional repressor that consists of three isoforms, Snail1, Snail2, and Snail3. Among them, Snail1 and Snail2 are activated in the EMT during development, fibrosis, and cancer. The upregulation of Snail1 is found in many different types of cancer such as gastric, colorectal, and prostate cancer.[17-19] In addition, the overexpression of Snail1 enhanced the motility and invasion of prostate cancer cells, and the silencing of Snail remarkedly suppressed the adhesion, migration, and invasion of Hep-2 cells.[19] Further study revealed that the knockdown of Snail blocked the EMT, which was accompanied by the downregulation of the expression of MMP-2, MMP-9, vimentin, N-cadherin, and fibronectin.[19] Moreover, Snail expression was demonstrated at different stages of kidney fibrosis, and the reactivation of Snail-induced renal fibrosis[20] (Figure 2). Furthermore, hypoxia-inducible factor 1α (HIF-1α) mediated EMT by regulating Snail and the β-catenin signaling pathway in early pulmonary fibrosis induced by paraquat.[21] Based on these findings, it was suggested that Snail played a key role in the EMT during fibrosis and cancer, and the targeted inhibition of Snail expression might be an effective therapy to treat fibrosis and tumors.

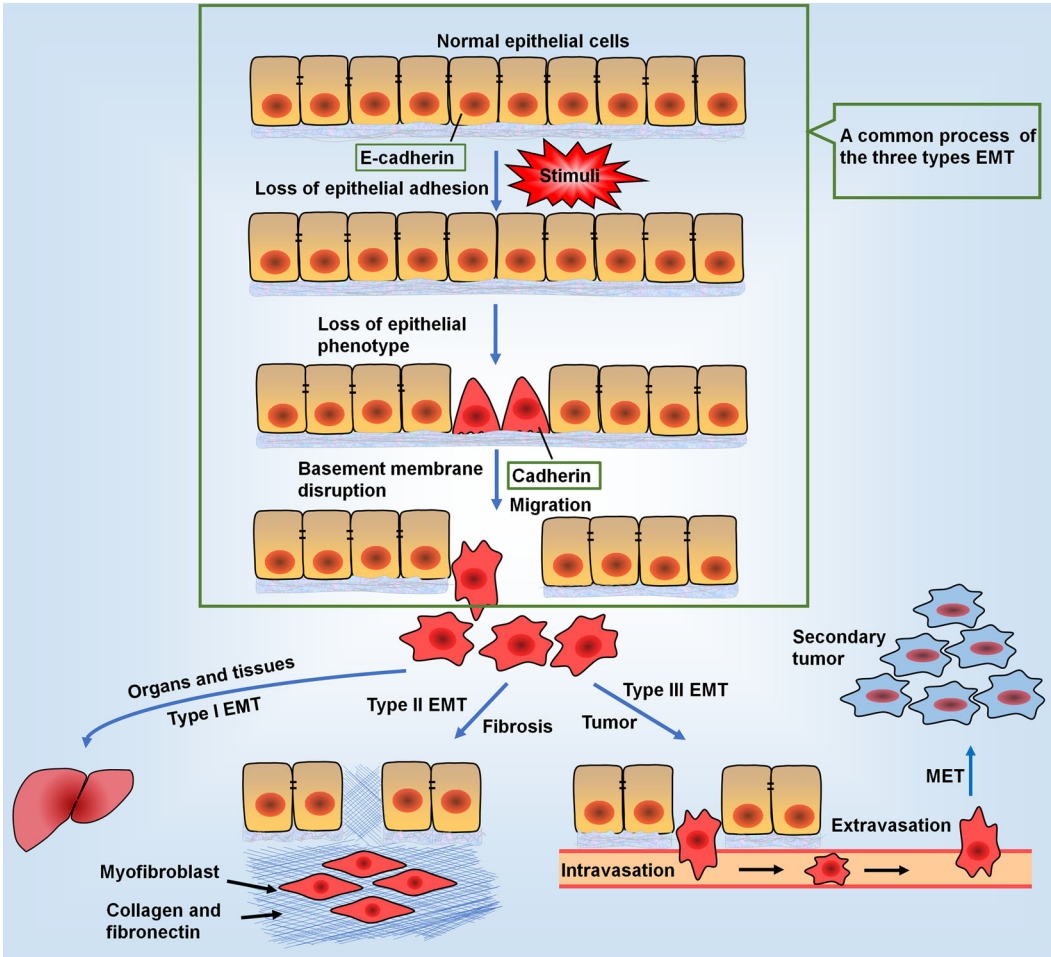

FIGURE 1 Cellular events during EMT. Under normal conditions, epithelial cells exist as single cell layers or multilayers and communicate with each other via specialized intercellular junctions including desmosomes, subapical tight junctions, adherens junctions, and scattered gap junctions. Once epithelial cells are damaged, the epithelial cell-cell junctions are dissolved, and the epithelial cells lose their apical-basal polarity and acquire a front-rear polarity. In addition, the cytoskeletal architecture is reorganized, and the expression of E-cadherin is replaced by the expression of N-cadherin, which contributes to cell motility and invasiveness. Then, the basement membrane is dissolved. During embryonic genesis, epithelia and mesenchymal cells mutually transform via EMT and MET, which is characterized as type I EMT and is critical for embryonic development and organ formation. In type II EMT, the mesenchymal-like cells are then transformed into myofibroblasts, which produce excessive collagen leading to fibrosis. In type III EMT, mesenchymal-like cells migrate along with the circulatory system to a secondary location, where the migratory cells form a secondary tumor via MET. The green pane indicates a common process in the three types of EMT that can be targeted to treat both fibrosis and tumor. EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition [Color figure can be viewed at wileyonlinelibrary.com]

Metformin is a first-line drug for treating type II diabetes mellitus that has shown a therapeutic effect on many cancers. Further study revealed that metformin increased the expression of E-cadherin, miR-200a, miR-200c, and miR-429 and decreased the expression of miR-34a, vimentin, Snail1 and ZEB1 in transforming growth factor-β (TGF-β)-induced EMT in the colorectal cancer cell lines SW480 and HCT-116 (Table 1).[57] In addition, some compounds derived from natural products have also shown significant intervention in fibrosis and tumors by targeting Snail (Table 1). Toosendanin, a triterpenoid isolated from *Melia toosendan* Sieb. et Zucc (Meliaceae), is

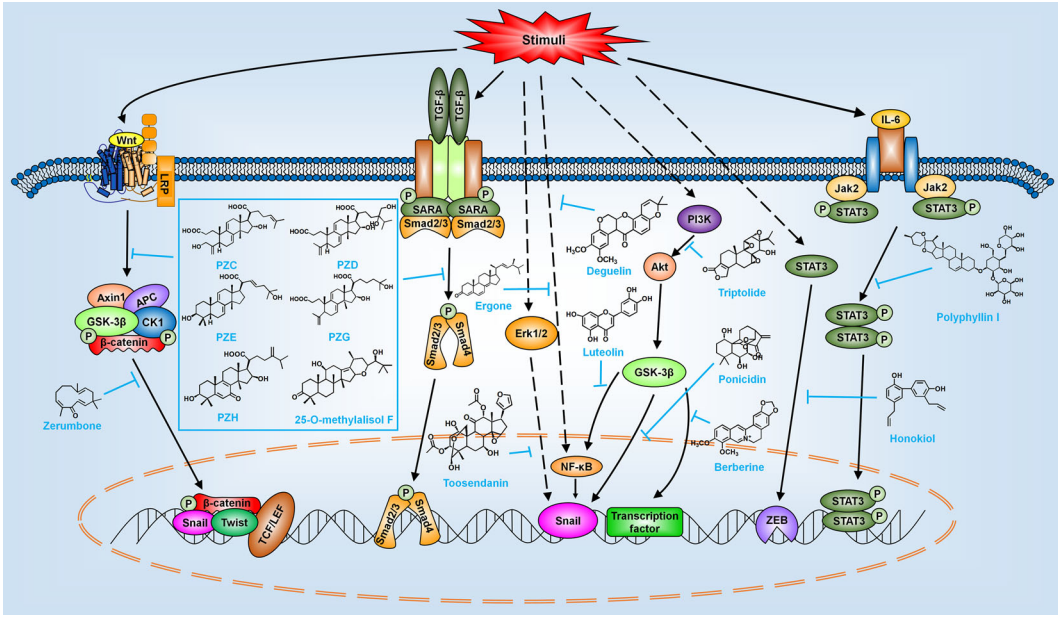

FIGURE 2 The molecular mechanisms of EMT and compounds from natural products that suppress EMT. EMT mediators, including the transcription factors Snail, ZEB and STAT3 and the signaling pathways NF-κB, Wnt/β-catenin, TGF-β1/Smad, and PI3K/Akt, are presented. Small molecules used for treatment and their targets are presented. Akt, RAC-α serine/threonine-protein kinase; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; GSK3β, glycogen synthase kinase-3β; JAK2, Janus kinase 2; IL-6, interleukin-6; NF-κB, nuclear factor κB; PI3K, phosphatidylinositol 3-kinase; STAT3, signal transducer and activator of transcription 3; ZEB, zinc-finger E-box-binding [Color figure can be viewed at wileyonlinelibrary.com]

used to prevent and control agricultural pests.[97] Recently, it was reported that toosendanin significantly inhibited TGF-β1-induced EMT in lung cancer cells via the extracellular signal-regulated kinase (ERK)/Snail pathway and suppressed EMT and tumor growth in pancreatic cancer by deactivating the RAC-α serine/threonine-protein kinase (Akt)/mechanistic target of rapamycin (mTOR) pathway (Figure 2), which suggests that toosendanin is a promising pharmacological agent for the treatment of cancer.[22,23] A recent study revealed that neferine enhanced oxaliplatin sensitivity by inhibiting EMT via the Snail pathway.[19] In addition, ponicidin is a major diterpenoid compound extracted from *Rabdosia rubescens* (Hemsl.) Hara that exhibited a therapeutic effect on TNF-α-induced EMT and the metastasis of colorectal cancer by targeting the Akt/glycogen synthase kinase-3 β (GSK3β)/Snail pathway[31] (Figure 2). Moreover, ferulic acid is a bioactive component derived from *Ligusticum chuanxiong* Hort that suppressed EMT induced by TGF-β1 via inhibiting the Smad/integrin-linked kinase/Snail signaling pathway in a renal proximal tubular epithelial cell line (NRK-52E), suggesting that ferulic acid might be potent fibrosis antagonist.[98]

2.1.2 | ZEB transcription factors

The two ZEB family members, ZEB1 and ZEB2, are transcriptional inhibitors that are involved in cell proliferation, migration, invasion, and apoptosis. Extensive studies have confirmed that ZEB1 is upregulated in the EMT and plays a key role in the development of tumors and fibrosis.[99,100] It was reported that the Np63-miR-205 axis increased epithelial marker gene expression and decreased mesenchymal marker gene expression in oral squamous cell carcinoma by downregulating ZEB1 and ZEB2.[101] Moreover, the heterogeneous expression of ZEB1 induced by EMT played an important role in metastasis through the regulation of miR-200c.[102] In addition, miR-302a-3p exerted a protective role via inhibiting ZEB1 and EMT in diabetic kidney disease.[103] These results suggest that

TABLE 1 Anti-EMT effects of small molecules

Compound	Compound type	Source	Disease	Signaling pathways	References
Toosendanin	Terpene	*Melia toosendan* Sieb. et Zucc (Meliaceae)	Lung cancer cells, pancreatic cancer	ERK/Snail, Akt/mTOR	22,23
Betulinic acid	Terpene	*Betula spp.*	Melanoma	AMPK	24
Codonolactone	Terpene	*Atractylodes Lancea* (Thunb.) DC.	Breast cancer cells	TGF-β	25
Zerumbone	Terpene	*Zingiber* Zerumbet (L.) Smith	Colorectal cancer cells	β-Catenin	26
Triptolide	Terpene	*Tripterygium wilfordii* Hook F	Diabetic kidney disease, IPF	PI3K/Akt, TGF-β	2728
Poricoic acid ZC Poricoic acid ZD Poricoic acid ZE	Terpene	*Poria cocos* (Polyporaceae)	Renal fibrosis	Wnt/β-catenin, TGF-β1	29
Poricoic acid ZG Poricoic acid ZH	Terpene	*Poria cocos* (Polyporaceae)	Renal fibrosis	Wnt/β-catenin, TGF-β1	29
25-O-methylalisol F	Terpene	*Alisma orientale* (Sam.) Juzep	Renal fibrosis	Wnt/β-catenin, TGF-β1	30
Alisol B 23-acetate	Terpene	*Alisma orientale (Sam.) Juzep*	Renal fibrosis	Wnt/β-catenin	30
Ponicidin	Terpene	*Rabdosia rubescens* (Hemsl.) Hara	Colorectal cancer cells	Akt/GSK3β/Snail	31
Tanshinone IIA	Terpene	*Salvia miltiorrhiza*	Bladder cancer cells, lung fibrosis	STAT3-CCL2, TGF-β/Smad	3233
Simvastatin	Terpene		Ec9706-R cells	PTEN/PI3K/Akt	34
Oridonin	Terpene	*Rabdosia rubescens* (Hemsl.) Hara	Osteosarcoma	TGF-β1/Smad2/3	35
Icaritin	Flavonoid	*Epimedium genus*	Glioblastoma cells	PTEN/Akt/HIF-1α,	36
Luteolin	Flavonoid	*Salvia tomentosa*	Gastric cancer, lung cancer cells, lung fibrosis	Notch, PI3K/Akt-NF-κB-Snail	37,38
Silibinin	Flavonoid	*Silybum marianum*	Bladder cancer	β-Catenin/ZEB1	39
Rhamnetin and Cirsiliol	Flavonoid	Cloves and berries, *Cirsium lineare* (Thunb.) Sch.-Bip.	Non-small-cell lung cancer cells	Notch1	40
Nobiletin	Flavonoid	*Citrus depressa*	Human non–small-cell lung cancer cells	Notch1, TGF-β1/Smad	41,42
Deguelin	Flavonoid	*Derris trifoliata*	Pancreatic cancer cells	NF-κB	43
Quercetin	Flavonoid	Fruits, vegetables and beverages	Pancreatic cancer cells, renal fibrosis	STAT3, miR-21	44,45

(Continues)

TABLE 1 (Continued)

Compound	Compound type	Source	Disease	Signaling pathways	References
Isoviolanthin	Flavonoid	*Dendrobium officinale*	Hepatocellular carcinoma cells	TGF-β1/Smad, PI3K/Akt/mTOR	[46]
3,6-Dihydroxyflavone	Flavonoid	Vegetables and fruits	Breast cancer cells	Notch	[47]
[58]Berberine	Alkaloid	*Berberis vulgaris*	Diabetic nephropathy, melanomas	PI3K/Akt and RARα/RARβ, Notch/Snail	[48,49]
Nicotine	Alkaloid	*Nicotiana rustica* L.	Non-small-cell lung cancer cells	MiR-99b and miR-192	[50]
Sophocarpine	Alkaloid	*Sophora alopecuroides* L.	Head and neck cancer, hepatocellular carcinoma	MiR-21, Akt/GSK3β/β-catenin	[51,52]
Evodiamine	Alkaloid	*Evodia rutaecarpa* (Juss.) Benth.	Rat renal proximal tubular epithelial cells	PPARγ and Smad	[53]
Caffeine	Alkaloid	Coffee	Hela cells, liver fibrosis	Serine/arginine-rich splicing factor 3, Snail and Nrf2	[54,55]
Neferine	Alkaloid	*Nelumbo nucifera* Gaertn.	Hepatocellular carcinoma	Snail1	[56]
Metformin	Alkaloid		Colorectal cancer cell lines SW480 and HCT-116	Snail1	[57]
Decitabine	Alkaloid		Non-small-cell lung cancer PC9 cells	MiR-200/ZEB	[58]
Sepantronium bromide	Alkaloid		Glioblastoma	STAT3	[59]
Trichostatin A	Alkaloid		Lung fibrosis	Akt	[60]
Ubenimex	Alkaloid		Renal cell carcinoma	Akt	[61]
Galunisertib	Alkaloid		Human hepatocellular carcinoma cell lines	TGFβRI	[62]
GW788388	Alkaloid		Renal fibrosis	TGFβRI	[63]
Oxymatrine	Alkaloid		NRK-52E cells	TGF-β1/Smad	[64]
FH355	Alkaloid		Radioresistant esophageal cancer cell line	Wnt/β-catenin	[65]
DAPT	Alkaloid		Oral squamous cell carcinoma cell lines	Notch	[66]
RO4929097	Alkaloid		Cervical cancer cells	Notch	[67]
Losartan	Alkaloid		Hyperglycemia	RAS	[68]

(Continues)

TABLE 1 (Continued)

Compound	Compound type	Source	Disease	Signaling pathways	References
Curcumin	Phenol	*Cnidium monnieri* (L.) Cuss.	Pancreatic cancer cells, breast cancer cells, intestinal fibrosis, bladder cancer	Wnt/β-catenin, c-Met/PI3K/Akt/mTOR, PPARγ, NF-κB-Snail, miR-34a	69-72
Resveratrol	Phenol	*Vaccinium* shrubs	HCT-116 colorectal cancer cells, gastric cancer, renal fibrosis, lung fibrosis	PTEN/Akt, miR-200c, TGF-β, p38-MAPK, TGF-β	73-76
Hispolon	Phenol	*Phellinus linteus* (Berkeley and Curtis) Teng	Human epithelial cancer cells	TGF-β-Snail/Twist	77
Honokiol	Phenol	*Magnolia grandiflora* L.	Breast cancer, renal cancer cells	STAT3/ZEB1/E-cadherin, LKB1/miR-34a, miR-141/ZEB2	78-80
Ergone	Steride	*Polyporus umbellatus* (Pers.) Fries	Renal fibrosis	Wnt/β-catenin	81
Polyphyllin I	Steride	*Paris polyphylla*	Prostate cancer, lung cancer cells	IL-6/STAT3, CIP2A/PP2A/ERK, CIP2A/PP2A/Akt	82,83
Telocinobufagin	Steride	Chan Su (*Venenum Bufonis*)	Breast cancer cells	PI3K/Akt/ERK/Snail	84
Thymoquinone	Quinone	*Nigella sativa*	Renal cell carcinoma, cervical cancer cells, prostate cancer cells, gastric cancer cells	Twist1 and ZEB1, LKB1/AMPK, TGF-β/Smad2/3, PI3K/Akt/mTOR	85-88
α-Mangostin	Xanthon	*Garcinia mangostana* L.	Pancreatic cancer cells	PI3K/Akt	89
Pterostilbene	Stilbenoid	Blueberries	Breast cancer stem cells, renal fibrosis	NF-κB/miR-488, TGF-β1	90,91
Osthole	Coumarin	*Cnidium monnieri* (L.) Cuss	Lung cancer A549 cells, prostate cancer	NF-κB/Snail, miR-23a-3p	92,93
Vitamin D			Human bronchial epithelial cells	TGF-β1	94
Salinomycin	Polyketide		Epithelial ovarian cancer cells	Wnt/β-catenin	95
Emodin	Anthraquinone	*Polygonum cuspidatum*	Alveolar epithelial cells	Notch	96

Abbreviations: Akt, RAC-α serine/threonine-protein kinase; AMPK, adenosine 5′-monophosphate (AMP)-activated protein kinase; CCL2, chemokine (C-C motif) ligand 2; ERK, extracellular signal-regulated kinase; HIF-1α, hypoxiainducible factor 1α; IL-6, interleukin-6; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PPAR, peroxisome proliferator-activated receptor; PTEN, phosphatase and tensin homologue; RAR, retinoic acid receptor; STAT3, signal transducer and activator of transcription 3.

various mediators contribute to EMT via the ZEB signaling pathway, suggesting that ZEB is a promising target for the treatment of fibrosis and tumors.

Decitabine is a drug used to treat myelodysplastic syndromes that inhibited EMT by regulating the miR-200/ZEB signaling pathway in non–small-cell lung cancer PC9 cells.[58] In addition, a phase Ib/II clinical trial revealed that low-dose decitabine enhanced the efficacy of immunotherapy in patients with drug-resistant relapsed/refractory alimentary tract cancer, making it an attractive therapy for cancers.[104]

Silibinin, a bioactive component from *Silybum marianum* (L.) Gaertn., exhibited anticancer properties in multiple types of cancer, such as bladder and lung cancer (Table 1). Recent studies revealed that silibinin reversed EMT by inhibiting the expression of ZEB1, vimentin, and MMP-2 as well as the transactivation of β-catenin in bladder cancer metastasis.[39] Furthermore, the combined treatment of silibinin with trichostatin A (an inhibitor of histone deacetylases) or decitabine suppressed EMT in non–small-cell lung cancer.[105] These studies suggest that silibinin is an important candidate anticancer drug. Honokiol was extracted from the seed cones of *Magnolia grandiflora* L. and showed a therapeutic effect on various cancers. Honokiol effectively inhibited EMT in breast cancer through the STAT3/ZEB1/E-cadherin axis (Figure 2) and reversed EMT in renal cell carcinoma via miR-141/ZEB2 (Table 1).[78,79]

2.1.3 | STAT3

STAT3, a member of the STAT protein family, can be phosphorylated as a transcription factor and plays a key role in various cellular processes, including cell growth, apoptosis, and differentiation. Hypoxia is a key mediator that induces EMT during tumor initiation and metastasis, and STAT3 promotes HIF-1α expression to induce EMT by binding to the promoter of HIF-1α. In addition, STAT3 was identified as a positive regulator that aggravated TGF-β1-induced EMT.[106] In particular, the JAK2/STAT3 signaling pathway had a significant effect on the EMT in multiple cancers.[107,108] In addition, STAT3 cooperated with other transcription factors promoting EMT, such as Twist and ZEB1.[109] For example, the expression of p-STAT3 (Tyr-705) and ZEB1 was positively associated with metastasis, and they cooperatively enhanced EMT in colorectal carcinoma.[110] Moreover, STAT3 was upregulated in TGF-β1-induced EMT during renal fibrosis, implying that STAT3 is an innovative target for the prevention of fibrosis.[111] Furthermore, there are many mediators that induce EMT through the activation of STAT3, such as Pin1, HOXB8, miR-30d, and IL-6.[112-115]

Sepantronium bromide is an inhibitor of survivin that exhibits anticancer properties in multiple cancer types. A recent study revealed that sepantronium bromide reduced the invasion of glioblastoma induced by radiation and reversed EMT by targeting STAT3.[59]

Tanshinone IIA is a major bioactive component from the famous medical herb *Salvia miltiorrhiza* that was reported to attenuate the proliferation of bladder cancer cells (Table 1). Further study revealed that tanshinone IIA suppressed EMT in bladder cancer cells via the modulation of the STAT3-CCL2 signaling pathway.[32] In addition, tanshinone IIA blocked EMT by regulating the TGF-β/Smad pathway in peritoneal fibrosis.[116] From these data, it was suggested that compounds that target EMT might have both antifibrotic and anticancer properties. In addition, polyphyllin I, a steroidal saponin derived from *Paris polyphylla*, has shown anti inflammatory and anticancer properties. It was suggested that polyphyllin I, which reversed EMT by modulating the IL-6/STAT3 pathway, served as a novel solution to conquer EGFR-TKI resistance in non–small-cell lung cancer [82] (Figure 2). Therefore, combined treatment with polyphyllin I and erlotinib is a promising therapy for lung cancer patients to strengthen drug efficacy and reduce drug resistance.[82] The other compound, quercetin, is a flavonoid widely distributed in fruits, vegetables, and beverages that shows antioxidative, anti inflammatory, and anticancer properties. Quercetin reversed IL-6-induced EMT in pancreatic cancer cells through STAT3.[44] Collectively, the data indicate that the use of compounds targeting STAT3 might be an effective approach for curing fibrosis and cancer.

2.2 | Targeting signaling pathways against EMT by small molecules

Many signaling pathways, such as the TGF-β1, nuclear factor-κB (NF-κB), Wnt, Akt, peroxisome proliferator-activated receptor (PPAR), and Notch pathways, and the renin-angiotensin system (RAS) contribute to the EMT. Targeting these signaling pathways may be effective for the treatment of fibrosis and tumors, and many small molecules that target these signaling pathways reverse EMT in fibrosis and tumors.

2.2.1 | TGF-β1 signaling pathway

TGF-β1 plays a crucial role in various cellular functions, including cell growth, proliferation, differentiation, and apoptosis, and is considered a key mediator in EMT during the processes of tumor formation and fibrosis.[117] Many components contribute to EMT through the TGF-β1 signaling pathway, which indicates that the inhibition of the TGF-β1 signaling pathway may be effective in the treatment of cancer and fibrosis. Several excellent reviews have discussed the role of the TGF-β1 signaling pathway in tumors and fibrosis well.[117,118] Here, we present several important small molecules that suppress EMT in tumors and fibrosis by targeting the TGF-β1 signaling pathway (Table 1).

Galunisertib, also known as LY2109761, is a TGF-β receptor kinase inhibitor that specifically downregulated the phosphorylation of Smad2 and upregulated E-cadherin expression in cultured human hepatocellular carcinoma cell lines, implying that it could suppress the EMT.[119] Galunisertib is now in ongoing clinical trials in patients with glioblastoma, pancreatic cancer, and hepatocellular carcinoma.[62] Nobiletin is a flavonoid compound isolated from *Citrus depressa* that suppressed EMT by antagonizing the TGF-β1/Smad signaling pathway in human non–small-cell lung cancer cells.[42] In addition, oridonin is a diterpenoid from *Rabdosia rubescens* (Hemsl.) Hara that inhibited EMT via blocking TGF-β1/Smad2/3 in osteosarcoma.[35] Moreover, GW788388 is a novel inhibitor of TGF-β type I receptor that inhibited TGF-β-induced EMT and fibrogenesis in db/db mice that showed significant diabetic nephropathy.[63] Furthermore, oxymatrine, a bioactive alkaloid from *Sophora japonica* L., alleviated EMT induced by high glucose through inhibiting the TGF-β1/Smad signaling pathway in NRK-52E cells, indicating that oxymatrine might be a therapeutic agent for diabetic nephropathy.[64] Isoviolanthin, a flavonoid isolated from *Dendrobium officinale* Kimura et Migo, suppressed TGF-β1-induced EMT through inhibiting the TGF-β1/Smad and phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signaling pathways in hepatocellular carcinoma cells.[46] In addition, vitamin D, a well-known inhibitor of EMT, inhibited EMT by negatively regulating the TGF-β1 signaling pathway in human bronchial epithelial cells, and MART-10 (a vitamin D analogue) suppressed metastasis via downregulating EMT in pancreatic cancer cells.[94,120]

2.2.2 | NF-κB signaling pathway

The NF-κB signaling pathway is widely involved in multiple cellular activities, such as cell proliferation, apoptosis, invasion, and inflammation. NF-κB plays a vital role in the inflammation of tissue fibrosis, and inhibiting NF-κB activity reduced inflammation and enhanced recovery from CCl_4-induced liver fibrosis.[121] In addition, NF-κB contributed to inflammation, apoptosis, growth, migration, and invasion of cancer cells.[122,123] Recently, it was found that the mediator of RNA polymerase II transcription, subunit 28 (MED28) modulated EMT through NF-κB in human breast cancer cells, which suggests that the NF-κB signaling pathway also plays a key role in the process of EMT.[124] Therefore, targeting the NF-κB signaling pathway may be a good choice to treat fibrosis and tumors.

Osthole, a dominant component in *Cnidium monnieri* (L.) Cuss., exhibited various biological activities including neuroprotective, osteogenic, cardiovascular protective, immunomodulatory, hepatoprotective, and antimicrobial effects. Osthole was found to block TGF-β1-induced EMT, adhesion, migration, and invasion by the inactivation of the NF-κB/Snail pathways in A549 cells (Table 1).[92] In addition, osthole also attenuated insulin-like growth factor-1-induced EMT by the PI3K/Akt pathway and inhibited hepatocyte growth factor-induced EMT via the c-Met/Akt/mTOR pathway in human brain cancer cells.[125] Pterostilbene is a stilbene containing in blueberries hat effectively

blocked the EMT in breast cancer stem cells by the NF-κB/miR-488 circuit.[90] Moreover, pterostilbene negatively regulated EMT and inhibited triple-negative breast cancer metastasis via inducing the expression of miR-205.[126]

The sclerotia of *Polyporus umbellatus* (Pers.) Fries is widely used to promote urination and prevent dampness.[127] Our previous studies systematically demonstrated that ergosta-4,6,8(14),22-tetraen-3-one (ergone) isolated from *Polyporus umbellatus* (Pers.) Fries showed significant antitumor, diuretic, and renoprotective effects.[128-135] Our recent study demonstrated that ergone inhibited NF-κB signaling and α-SMA expression in 5/6 nephrectomised and unilateral ureteral obstruction rats[136,137] (Figure 2 and Table 1).

2.2.3 | Wnt signaling pathway

The Wnt signaling pathway is an evolutionarily conserved developmental signaling cascade that plays a critical role in regulating organ development and tissue homeostasis. Leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5) is a novel functional marker in glioma stem cells that promotes EMT by activating the Wnt/β-catenin signaling pathway.[138] Sry-like high-mobility group box 8 regulated cancer stem-like properties and cisplatin-induced EMT by the Wnt/β-catenin signaling pathway in tongue squamous cell carcinoma.[139] In addition, bone marrow mesenchymal stromal cells suppressed EMT by inhibiting the Wnt/β-catenin signaling pathway in silica-induced pulmonary fibrosis.[140] Our previous study showed the activation of the canonical Wnt/β-catenin signaling pathway accompanied by the upregulation of proinflammatory and pro-oxidative protein expression in the NF-κB signaling pathway and downregulation of the anti-inflammatory Nrf2 signaling pathway in patients with chronic kidney disease compared with the Nrf2 signaling pathway in healthy controls.[141]

Many compounds inhibit the Wnt signaling pathway, and these compounds may suppress EMT in cancer and fibrosis (Table 1).[142] FH535, a β-catenin/Tcf inhibitor, not only increased radio-sensitivity but also suppressed EMT in the radioresistant KYSE-150R esophageal cancer cell line, which indicated that inhibitors of the Wnt signaling pathway might be effective anticancer agents with the potential to be anticancer drugs.[65] In addition, it was reported that FH535 alleviated multiple types of cancer, including colorectal cancer, gastric cancer, and hepatocellular carcinoma.[143-145] Isoquercitrin, a bioactive flavonoid from *Bidens bipinnata L.*, inhibited the Wnt/β-catenin signaling pathway and hepatocyte growth factor/scatter factor-induced EMT in NBT-II cells.[146] In addition, salinomycin was previously used as an antibiotic and also showed significant anticancer activity by suppressing EMT.[95,147,148] Salinomycin-inhibited EMT by suppressing the Wnt/β-catenin signaling pathway in epithelial ovarian cancer cells, indicating that small molecules targeting the Wnt/β-catenin signaling pathway might have anticancer properties by reversing EMT.[95] *Poria cocos* (Polyporaceae) is a well-known fungus that exhibits an effective therapeutic effect to improve kidney function in clinic.[149,150] Our previous studies have confirmed that extracts of the surface layer of *Poria cocos* show remarkable antihyperlipidemic, diuretic, and renoprotective effects.[151-158] Recently, our group isolated more than 90 triterpenoid compounds from the surface layer of *Poria cocos*, some of which exhibited significant antifibrotic properties.[159-161] New triterpenoids, including poricoic acid ZC, poricoic acid ZD, and poricoic acid ZE, significantly downregulated the expression of Wnt1, active β-catenin, Snail, Twist, MMP-7, PAI-1, and FSP1 in HK-2 cells induced by TGF-β1 and angiotensin II and mice with unilateral ureteral occlusion[29] (Figure 2 and Table 1). Moreover, new triterpenoids, including poricoic acid ZG and poricoic acid ZH, improved renal fibrosis by targeting the phosphorylation of Smad3 signaling and the Wnt/β-catenin signaling pathway[162] (Figure 2 and Table 1).

Alismatis rhizome (AR), the dried rhizome of *Alisma orientale* (Sam.) Juzep, exhibited diuretic, antihyperlipidemic, and renoprotective effects[163] that were also confirmed by our previous studies.[164-167] Our recent study demonstrated that triterpenoid was the main component of AR,[30] and further study showed that the novel tetracyclic triterpenoid 25-O-methylalisol F inhibited EMT by suppressing the Wnt/β-catenin signaling pathway as well as the phosphorylation of Smad3 signaling in both NRK-52E and NRK-49F cells[30] (Figure 2 and Table 1). Additionally, it was also observed that ergone inhibited extracellular matrix accumulation in HK-2 cells and attenuated podocyte injury through inhibiting the activation of the Wnt/β-catenin signaling pathway induced by

angiotensin II.[81] Taken together, these data indicate that tetracyclic triterpenoid and steroid compounds show significant antifibrotic properties in renal fibrosis.

2.2.4 | Akt signaling pathway

Akt (also known as protein kinase B or Rac) is a serine/threonine-specific protein kinase that plays a key role in various cellular activities. Many cellular signals are transduced through the Akt signaling pathway, and Akt is involved in EMT in cooperation with other proteins. For example, tripartite motif-containing 14 is an oncogene that regulated EMT and the metastasis of human gastric cancer by activating Akt signaling.[168] M3 muscarinic acetylcholine receptors regulated EMT, perineural invasion, and metastasis in cholangiocarcinoma via the Akt pathway.[169] Canopy homologue 2 promoted EMT via activating the Akt/GSK3 pathway in non–small-cell lung cancer.[170] The Akt signaling pathway mediated cigarette-induced EMT in lung cancer.[171] In addition, Akt also promoted EMT cooperation with miRNAs. MiR-944 inhibited EMT and the metastasis of gastric cancer by the metastasis-associated in colon cancer 1 (MACC1)/Met/Akt signaling pathway.[172] MiR-1296 inhibited EMT and the metastasis of hepatocellular carcinoma via the serine/threonine-protein kinase 1/PI3K/Akt signaling pathway.[173] Taken together, these data suggest that Akt plays a key role in EMT cellular signal transduction and that targeting Akt might be an effective approach to treat fibrosis and tumors (Table 1).

Simvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor that was originally used to treat cardiovascular diseases. Recently, it was reported that simvastatin had a therapeutic effect in several cancers. The administration of simvastatin suppressed EMT through the phosphatase and tensin homologue (PTEN)/PI3K/Akt pathway in EC9706-R cells, suggesting a new therapeutic function for simvastatin in cancers.[34] Trichostatin A, a histone deacetylase inhibitor, is an antifungal antibiotic. In addition to its antibiotic properties, trichostatin A alleviated EMT in bleomycin-induced lung injury in mice via inhibiting the Akt signaling pathway.[60]

Ubenimex inhibits multiple proteases, including arginyl aminopeptidase, leukotriene A_4 hydrolase, alanyl aminopeptidase, and leucyl/cysteinyl aminopeptidase, a membrane dipeptidase used to treat acute myelocytic leukemia and lymphedema. Ubenimex alleviated acquired sorafenib (a first-line anticancer drug) resistance in renal cell carcinoma via suppressing the Akt pathway.[61]

Luteolin is widely distributed in plants and has shown anti inflammatory, antioxidant, antimicrobial, and antitumor properties. Luteolin attenuated TGF-β1-induced EMT by mediating the PI3K/Akt/NF-κB-Snail pathway in lung cancer cells[37] (Figure 2). In addition, luteolin attenuated the progression of gastric cancer by reversing EMT via the Notch signaling pathway.[38] Moreover, luteolin also suppressed the metastasis of triple-negative breast cancer via blocking EMT by the downregulation of β-catenin.[174] Furthermore, luteolin suppressed EMT by downregulating the expression of cyclic AMP-responsive element binding protein 1[175] in colorectal cancer cells.[176] Collectively, luteolin showed therapeutic effects in both tissue fibrosis and tumors through various signaling pathways and might be a promising candidate to treat fibrosis and tumors.

α-Mangostin derived from the pericarp of the mangosteen fruit has been shown to have various cellular functions, such as arresting the cell cycle, inhibiting cell viability, inducing apoptosis, and differentiation, reducing inflammation and decreasing adhesion. α-Mangostin suppressed viability and EMT by downregulating the PI3K/Akt pathway in pancreatic cancer.[89] Icaritin, a hydrolytic product of icariin that is isolated from members of the *Epimedium genus*, induced the trans-differentiation of embryonic stem cells into cardiomyocytes, prevented steroid-associated osteonecrosis and stimulated neuronal differentiation.[36] Icaritin inhibited invasion and EMT via targeting the PTEN/Akt/HIF-1α signaling pathway.[36]

2.2.5 | PPARγ signaling pathway

PPAR belongs to the nuclear hormone receptor superfamily and consists of three isoforms including PPARα, PPARβ/δ, and PPARγ. PPAR played essential roles in the regulation of cellular differentiation, development,

metabolism, and tumorigenesis; in particular, PPARγ exerted a protective role in the development of fibrosis and tumors. A recent study revealed that the activation of PPARγ attenuated cardiac fibrosis, which was mediated by the downregulation of EMT and the TGF-β/ERK pathway.[177] In addition, the overexpression of miR-130b promoted EMT in glioma cells and human hepatocellular carcinoma, and PPARγ was identified as a functional target of miR-130b, which was inversely correlated with PPARγ.[178] Moreover, it was reported that the PPARγ agonist pioglitazone suppressed fibrotic changes in primary monkey retinal pigment epithelial cells by inhibiting the TGF-β signaling pathway.[179] Collectively, these results suggest that PPARγ might be a therapeutic target against fibrosis and tumors (Table 1).

Evodiamine from *Evodia rutaecarpa* (Juss.) Benth. exerts anti inflammatory, antiobesity, antianxiety, antiallergic, and anticancer effects. Evodiamine suppressed TGF-β1-induced EMT in NRK-52E cells via the PPARγ signaling pathway.[53] In addition, curcumin is an active component of *Curcuma longa* L. that exhibits antioxidant, antibacterial, antifungal, antiviral, anti inflammatory, antiproliferative, and anticarcinogenic properties. Curcumin had an antifibrotic effect in intestinal fibrosis and prevented the EMT by the PPARγ signaling pathway.[69]

2.2.6 | Notch signaling pathway

As a highly conserved cell signaling system, the Notch signaling pathway is widely involved in cell proliferation and differentiation during embryonic and adult development. Extensive studies have demonstrated that the Notch signaling pathway is also critical for EMT in tumorigenesis and fibrogenesis. The overexpression of Notch1-induced EMT in PC-3 cells, and claudin-1 contributed to EMT by the Notch signaling pathway in human bronchial epithelial cells.[180,181] In addition, Notch and TGF-β1 generated a reciprocal positive regulatory loop and cooperatively regulated EMT in epithelial ovarian cancer cells, which provided new insight into the mechanism of EMT.[182] Moreover, miR-34a downregulation induced by hypoxia enhanced EMT via the Notch signaling pathway in tubular epithelial cells, which indicated that the Notch signaling pathway is critical for EMT during fibrosis.[66] These cases suggest that a targeted intervention in the Notch signaling pathway might be an effective strategy to treat cancer and fibrosis.

DAPT, a γ-secretase inhibitor, decreased the expression of Snail and vimentin and increased E-cadherin expression in two oral squamous cell carcinoma cell lines, Tca8113 and CAL27, indicating that the targeted inhibition of the Notch signaling pathway might be a new therapeutic strategy to treat cancer.[183,184] Another γ-secretase inhibitor, RO4929097, not only inhibited EMT, invasion, and metastasis in cervical cancer HeLa and CaSki cells but also exerted significant therapeutic effects in patients with recurrent malignant glioma, cervical and colon cancer and advanced solid tumors in clinical trials.[67,185,186] 3,6-Dihydroxyflavone is ubiquitous in vegetables and fruits and blocks EMT in breast cancer cells through suppressing the Notch signaling pathway.[47] Moreover, luteolin inhibited EMT in gastric cancer by the Notch signaling pathway.[38] In addition, emodin is a main bioactive component of *Polygonum cuspidatum* that suppressed EMT in alveolar epithelial cells via the Notch signaling pathway. Therefore, it is a promising prospect in treating pulmonary fibrosis.[96] Furthermore, berberine was isolated from *Berberis vulgaris* and reversed EMT by blocking the Notch/Snail signaling pathway in mice with diabetic nephropathy.[48]

2.2.7 | RAS signaling pathway

The RAS signaling pathway not only regulates blood pressure and fluid balance but also is involved in many kinds of diseases, including cancer and fibrosis. Recently, emerging evidence has suggested that the RAS signaling pathway plays a key role in EMT during fibrosis and tumorigenesis. Angiotensin II promoted EMT by the interaction between hematopoietic stem cells and the stromal cell-derived factor-1/CXR4 axis in intrahepatic cholangiocarcinoma.[187] In addition, the overexpression of angiotensin II type 1 receptor induced EMT and promoted tumorigenesis in human breast cancer cells, and the silencing of angiotensin II type 1 receptor suppressed EMT that was induced by high glucose through inactivating the mTOR/p70s6k signaling pathway in the human proximal tubular epithelial HK-2

cell line.[188,189] Based on these results, it was suggested that suppressing RAS might be an effective therapy to treat cancer and fibrosis.

Losartan is an AT1R antagonist that improved renal fibrosis by suppressing EMT in rats with hyperglycemia.[68] Although many RAS inhibitors showed beneficial effects in tumors and fibrosis, few were reported to inhibit EMT in the treatment of cancer and fibrosis.[190,191]

2.3 | Targeting miRNA signaling pathways by small molecules

MiRNAs are endogenous small noncoding RNAs (19-25 nucleotides) that bind the 3′-untranslated region of messenger RNAs to regulate gene expression. Recently, many miRNAs have been found to promote or suppress EMT in fibrosis and tumors. For example, miRNA-497/Wnt3a/c-Jun regulated growth and EMT, and miR-497 served as a tumor suppressor in glioma cells.[192] Moreover, miR-205 inhibited tumor growth, invasion, and EMT via targeting semaphorin 4C in hepatocellular carcinoma.[193] Furthermore, the upregulation of miR-183-5p induced apoptosis and inhibited EMT, proliferation, invasion, and migration by the downregulation of ezrin in human endometrial cancer cells.[194] Collectively, EMT is inhibited by many miRNAs, including miR-145, miR-497, miR-145-5p, miR-138, miR-200a, miR-200b, miR-655, miR-30-5p, and miR-32.[195-201] In addition, EMT is also promoted by many miRNAs, including miR-221, miR-222, miR-214-3p, and miR-181a.[202-204]

The flavonoids rhamnetin from cloves, berries and cirsiliol from *Cirsium lineare* (Thunb.) Sch.-Bip. showed anti inflammatory and antitumor properties. Both rhamnetin and cirsiliol induced radio-senitization and inhibited EMT by miR-34a/Notch1 signaling in non–small-cell lung cancer cells.[40] Quercetin alleviated TGF-β1-induced fibrosis in HK-2 cells via downregulating miR-21 expression and upregulating PTEN and TIMP metallopeptidase inhibitor 3 (TIMP3) expression.[45] Sophocarpine from *Sophora alopecuroides* L. inhibited tumor progression and reversed EMT by targeting miR-21 in head and neck cancer.[51] In addition, sophocarpine exerted a profound antitumor effect through inhibiting EMT induced by TGF-β.[52] Zerumbone from *Zingiber zerumbet* (L.) Smith exhibited anti-inflammatory and anticancer properties. Recently, it was reported that zerumbone inhibited the β-catenin pathway via miR-200c to block EMT and cancer stem cells.[26] In addition, nicotine upregulated FGFR3 and RB1 and promoted EMT by the downregulation of miR-99b and miR-192 in non–small-cell lung cancer cells.[50] Moreover, osthole alleviated EMT-mediated metastasis by inhibiting miR-23a-3p.[93] Furthermore, resveratrol inhibited proliferation, invasion, and EMT via the upregulation of miR-200c in HCT-116 colorectal cancer cells.[73]

2.4 | Targeting RNA splicing protein signaling pathways by small molecules

RNA-binding proteins such as RNA-binding Fox protein 2 (Rbfox2), epithelial splicing regulatory protein 1 (ESRP1), and ESRP2 control the splicing of many gene transcripts and splice nascent RNAs to functionally and structurally different miRNAs to regulate the process of EMT. For example, bleomycin inhibited ESRP1 expression, leading to the increased alternative splicing of FGFR2 to its mesenchymal isoform IIIc, which induced EMT in lung fibrosis.[205] In addition, overexpressed ESRP1 contributed to EMT in ovarian cancer, inducing a cell-specific variant of CD44 and a protein-enabled homologue.[206] Moreover, Rbfox2 was upregulated during the EMT, and the depletion of Rbfox2 suppressed the expression of mesenchymal marker genes.[207]

Several studies have revealed that small molecules regulate the expression of RNA-binding proteins to mediate EMT. For example, caffeine, an alkaloid in tea and coffee, reduced p53α expression and upregulated p53β expression through altering the expression of serine/arginine-rich splicing factor 3 to regulate EMT.[54]

2.5 | Other novel mediators

Here, we present some novel mediators that contribute to EMT with the prospect of treating fibrosis and tumors. N-acetylglucosaminyltransferase, belonging to the family of glycosyltransferases, played a key role in EMT. Loss of

N-acetylglucosaminyltransferase I induced cell-cell adhesion, decreased cell migration and suppressed the expression of α-SMA, vimentin, and N-cadherin, suggesting the inhibition of EMT.[208] Moreover, N-acetylglucosaminyltransferase I alleviated EMT induced by TGF-β1 in human MCF-10A cells.[209]

Protein arginine methyltransferase 1 (PRMT1) mediates many essential cellular functions and plays an important role in cancer cell proliferation. Recent studies revealed that PRMT1 is a novel mediator of EMT, cancer cell migration, and invasion. Twist1 and E-cadherin are its substrates.[210] These findings strongly indicate that targeting PRMT1-mediated Twist methylation may be a new therapeutic strategy to treat fibrosis and tumors.

Histone H2A type 2-c (Hist2h2ac) was expressed in all breast cancers, and its expression was induced by EGF in the $CD24^{+}$/CD29hi/DC44hi cell subpopulation. Hist2h2ac silencing inhibited EGF-induced ZEB1 expression and E-cadherin downregulation, which suggested that Hist2h2ac is a novel regulator of EMT in breast cancer.[211]

EGF-like repeat and discoidin I-like domain-containing protein 3 (EDIL3) induced EMT and promoted hepatocellular carcinoma migration, invasion, and angiogenesis in vitro.[212] Furthermore, the overexpression of EDIL3 induced the activation of ERK and TGF-β signaling, and the deletion of EDIL3 suppressed EMT in lens epithelial cells through the TGF-β signaling pathway.[213] In addition, the cytoplasmic expression of interleukin-like EMT inducer (ILEI) is a potential marker of EMT and tumor development in colorectal cancer, and the overexpression of ILEI induced the downregulation of E-cadherin and the upregulation of vimentin.[214] Although the potential of these novel mediators in inducing tissue fibrosis and tumors has been investigated, no study has reported compounds targeting these mediators against fibrosis and tumors. Taken together, these results suggest that these novel mediators play key roles in the EMT, which will provide novel targets for small molecules in antifibrosis and antitumor research in the future.

3 | CONCLUDING COMMENTS

Both tissue fibrosis and tumors lead to high morbidity and mortality worldwide; thus, effective therapeutic strategies are urgently needed. Mounting studies have demonstrated that EMT plays a critical role in fibrosis and tumors, suggesting that drugs targeting EMT may be an effective therapy against fibrosis and tumors. Although TGF-β1 is a potent inducer of EMT, new targets are needed due to the controversial role of TGF-β1, which has been shown to have multiple beneficial roles in various bioactivities. As summarized above, myriad mediators, including many transcription factors (Snail, ZEB, and STAT3), signaling pathways (NF-κB, Wnt, Akt, and PPAR), RNA-binding proteins (ESRP1 and ESRP2) and miRNAs, regulate EMT. Targeting these mediators may be a novel therapeutic strategy for antifibrosis and antitumor treatment.

Many small molecules suppress EMT by targeting these mediators, including commercial drugs and compounds derived from natural products. In addition, these compounds that target EMT have shown anticancer effects on multiple types of cancer. For example, luteolin not only attenuated gastric cancer but also showed a therapeutic effect in lung cancer cells. Therefore, we concluded that compounds targeting EMT exerted anticancer effect in one type of cancer may be effective in other types of cancer. Moreover, curcumin targeted EMT and exhibited both anticancer and antifibrotic properties, which suggests that drugs targeting EMT may exhibit both antifibrotic and anticancer effects. Taken together, these data suggest that drugs targeting EMT not only have both antifibrotic and anticancer effects but also are active against multiple types of organ fibrosis and cancer, which may assist in discovering therapeutic drugs against fibrosis and cancer.

Small molecules are a huge resource for bioactive leading compounds, and it is important to discover novel bioactive compounds effectively and quickly. Here, we summarized several methods to investigate the prospect of natural products as drug candidates. First, molecular docking is used to predict the interaction between a ligand and target protein, and molecular docking-based virtual screening is helpful to discriminate active compounds from inactive ones. In addition, during lead optimization, calculations can quickly test modifications to the structures of known active compounds before synthesis. Therefore, computational methodologies can accelerate the discovery of bioactive compounds. Second, reverse pharmacokinetics is used for drug discovery from natural products with

defined clinical benefits. Reverse pharmacokinetics can be used to guide potential target tissues/organs/molecules, and then further physiologically relevant pharmacological models are designed to discover bioactive compounds and reveal their corresponding mechanisms.

It is worth noting that many compounds show low solubility, which limits their clinical efficiency and restricts their clinical use. Fortunately, there are multiple ways to enhance the bioavailability, such as cocrystallization and the formation of phospholipid complexes and nanoemulsions.[215-217]

Finally, based on the hypothesis that drugs targeting EMT have both antifibrotic and anticancer effects, many important mediators contributing to EMT have been discovered. Additionally, a great number of compounds suppress EMT in tumor and fibrosis by targeting these mediators. It is hoped that many new drugs are designed and developed in the future based on the aforementioned mediators to treat tumors and fibrosis.

ACKNOWLEDGMENTS

This study was supported by the National Natural Science Foundation of China (Grant Nos. 81673578, 81872985, 81603271).

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors were involved in the writing and revision of this manuscript and have provided final approval to submit.

ORCID

Ying-Yong Zhao http://orcid.org/0000-0002-0239-7342

REFERENCES

1. Wang C, Wang Z, Zhao T, et al. Optical molecular imaging for tumor detection and image-guided surgery. *Biomaterials*. 2018;157:62-75.
2. Aparicio LA, Blanco M, Castosa R, et al. Clinical implications of epithelial cell plasticity in cancer progression. *Cancer Lett*. 2015;366(1):1-10.
3. Wynn TA. Common and unique mechanisms regulate fibrosis in various fibroproliferative diseases. *J Clin Invest*. 2007;117(3):524-529.
4. Levin A, Tonelli M, Bonventre J, et al. Summit ISNGKH. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet*. 2017;390(10105):1888-1917.
5. Bohm M, Schumacher H, Teo KK, et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. *Lancet*. 2017;389(10085):2226-2237.
6. Rangarajan S, Bone NB, Zmijewskal AA, et al. Metformin reverses established lung fibrosis in a bleomycin model. *Nat Med*. 2018;24(8):1121-1127.
7. Davis FM, Stewart TA, Thompson EW, Monteith GR. Targeting EMT in cancer: opportunities for pharmacological intervention. *Trends Pharmacol Sci*. 2014;35(9):479-488.
8. Nakaya Y, Sheng G. EMT in developmental morphogenesis. *Cancer Lett*. 2013;341(1):9-15.
9. Zhang L, Wang X, lai M. Modulation of epithelial-to-mesenchymal cancerous transition by natural products. *Fitoterapia*. 2015;106:247-255.
10. Wynn TA. Cellular and molecular mechanisms of fibrosis. *J Pathol*. 2008;214(2):199-210.
11. Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010. *J Nat Prod*. 2012;75(3):311-335.

12. Chen DQ, Feng YL, Cao G, Zhao YY. Natural products as a source for antifibrosis therapy. *Trends Pharmacol Sci*. 2018;39(11):937-952.
13. Chen DQ, Hu HH, Wang YN, Feng YL, Cao G, Zhao YY. Natural products for the prevention and treatment of kidney disease. *Phytomedicine*. 2018;50:50-60.
14. Hu HH, Chen DQ, Wang YN, et al. New insights into TGF-β/Smad signaling in tissue fibrosis. *Chem Biol Interact*. 2018;292:76-83.
15. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol*. 2014;15(3):178-196.
16. Preisser L, Miot C, Le Guillou Guillemette H, et al. IL-34 and macrophage colony-stimulating factor are overexpressed in hepatitis C virus fibrosis and induce profibrotic macrophages that promote collagen synthesis by hepatic stellate cells. *Hepatology*. 2014;60(6):1879-1890.
17. Chen X, Li J, Hu L, et al. The clinical significance of snail protein expression in gastric cancer: a meta-analysis. *Hum Genomics*. 2016;10(S2):22.
18. Kwon CH, Park HJ, Choi JH, et al. Snail and serpinA1 promote tumor progression and predict prognosis in colorectal cancer. *Oncotarget*. 2015;6(24):20312-20326.
19. Osorio LA, Farfan NM, Castellon EA, Contreras HR. Snail transcription factor increases the motility and invasive capacity of prostate cancer cells. *Mol Med Rep*. 2016;13(1):778-786.
20. Boutet A, Esteban MA, Maxwell PH, Nieto MA. Reactivation of Snail genes in renal fibrosis and carcinomas—a process of reversed embryogenesis? *Cell Cycle*. 2007;6(6):638-642.
21. Zhu Y, Tan JT, Xie H, Wang JF, Meng XX, Wang RL. HIF-1α regulates EMT via the Snail and β-catenin pathways in paraquat poisoning-induced early pulmonary fibrosis. *J Cell Mol Med*. 2016;20(4):688-697.
22. Luo W, Liu X, Sun W, Lu JJ, Wang YT, Chen XP. Toosendanin, a natural product, inhibited TGF-1-induced epithelial-mesenchymal transition through ERK/Snail pathway. *Phytother Res*. 2018;32(10):2009-2020.
23. Pei Z, Fu W, Wang G. A natural product toosendanin inhibits epithelial-mesenchymal transition and tumor growth in pancreatic cancer via deactivating Akt/mTOR signaling. *Biochem Biophys Res Commun*. 2017;493(1):455-460.
24. Gheorgheosu D, Jung M, Oren B, et al. Betulinic acid suppresses NGAL-induced epithelial-to-mesenchymal transition in melanoma. *Biol Chem*. 2013;394(6):773-781.
25. Fu JJ, Ke XQ, Tan SL, et al. The natural compound codonolactone attenuates TGF-β1-mediated epithelial-to-mesenchymal transition and motility of breast cancer cells. *Oncol Rep*. 2016;35(1):117-126.
26. Dermani FK, Amini R, Saidijam M, Pourjafar M, Saki S, Najafi R. Zerumbone inhibits epithelial-mesenchymal transition and cancer stem cells properties by inhibiting the β-catenin pathway through miR-200c. *J Cell Physiol*. 2018;233(12):9538-9547.
27. Xue M, Cheng Y, Han F, et al. Triptolide attenuates renal tubular epithelial-mesenchymal transition via the miR-188-5p-mediated PI3K/Akt pathway in diabetic kidney disease. *Int J Biol Sci*. 2018;14(11):1545-1557.
28. Chen H, Chen Q, Jiang CM, et al. Triptolide suppresses paraquat induced idiopathic pulmonary fibrosis by inhibiting TGFB1-dependent epithelial mesenchymal transition. *Toxicol Lett*. 2018;284:1-9.
29. Wang M, Chen DQ, Chen L, et al. Novel inhibitors of the cellular renin-angiotensin system components, poricoic acids, target Smad3 phosphorylation and Wnt/β-catenin pathway against renal fibrosis. *Br J Pharmacol*. 2018;175(13):2689-2708.
30. Chen H, Yang T, Wang MC, Chen DQ, Yang Y, Zhao YY. Novel RAS inhibitor 25-O-methylalisol F attenuates epithelial-to-mesenchymal transition and tubulo-interstitial fibrosis by selectively inhibiting TGF-β-mediated Smad3 phosphorylation. *Phytomedicine*. 2018;42:207-218.
31. Zhang Z, Xu J, Liu B, et al. Ponicidin inhibits pro-inflammatory cytokine TNF-α-induced epithelial-mesenchymal transition and metastasis of colorectal cancer cells via suppressing the Akt/GSK-3β/Snail pathway. *Inflammopharmacology*. 2018:1-12. https://doi.org/10.1007/s10787-018-0534-5
32. Huang SY, Chang SF, Liao KF, Chiu SC. Tanshinone IIA inhibits epithelial-mesenchymal transition in bladder cancer cells via modulation of STAT3-CCL2 signaling. *Int J Mol Sci*. 2017;18(8):14.
33. Tang HY, He HY, Ji H, et al. Tanshinone IIA ameliorates bleomycin-induced pulmonary fibrosis and inhibits transforming growth factor-β-dependent epithelial to mesenchymal transition. *J Surg Res*. 2015;197(1):167-175.
34. Jin YY, Xu K, Chen QJ, et al. Simvastatin inhibits the development of radioresistant esophageal cancer cells by increasing the radiosensitivity and reversing EMT process via the PTEN-PI3K/Akt pathway. *Exp Cell Res*. 2018;362(2):362-369.
35. Sun Y, Jiang XB, Lu Y, et al. Oridonin prevents epithelial-mesenchymal transition and TGF-β1-induced epithelial-mesenchymal transition by inhibiting TGF-β1/Smad2/3 in osteosarcoma. *Chem Biol Interact*. 2018;296:57-64.
36. Xu B, Jiang CW, Han HX, et al. Icaritin inhibits the invasion and epithelial-to-mesenchymal transition of glioblastoma cells by targeting EMMPRIN via PTEN/AKt/HIF-1α signalling. *Clin Exp Pharmacol Physiol*. 2015;42(12):1296-1307.
37. Chen KC, Chen CY, Lin CJ, et al. Luteolin attenuates TGF-β1-induced epithelial-mesenchymal transition of lung cancer cells by interfering in the PI3K/Akt-NF-κB-Snail pathway. *Life Sci*. 2013;93(24):924-933.

38. Zang MD, Hu L, Fan ZY, et al. Luteolin suppresses gastric cancer progression by reversing epithelial-mesenchymal transition via suppression of the Notch signaling pathway. *J Trans Med*. 2017;15:11.
39. Wu KJ, Ning ZY, Zeng J, et al. Silibinin inhibits β-catenin/ZEB1 signaling and suppresses bladder cancer metastasis via dual-blocking epithelial-mesenchymal transition and stemness. *Cell Signal*. 2013;25(12):2625-2633.
40. Kang J, Kim E, Kim W, et al. Rhamnetin and cirsiliol induce radiosensitization and inhibition of epithelial-mesenchymal transition (EMT) by miR-34a-mediated suppression of Notch-1 expression in non-small cell lung cancer cell lines. *J Biol Chem*. 2013;288(38):27343-27357.
41. Gao XJ, Liu JW, Zhang QG, Zhang JJ, Xu HT, Liu HJ. Nobiletin inhibited hypoxia-induced epithelial-mesenchymal transition of lung cancer cells by inactivating of Notch-1 signaling and switching on miR-200b. *Pharmazie*. 2015;70(4):256-262.
42. Da CL, Liu YT, Zhan YY, Liu K, Wang RZ. Nobiletin inhibits epithelial-mesenchymal transition of human non-small cell lung cancer cells by antagonizing the TGF-β1/Smad3 signaling pathway. *Oncol Rep*. 2016;35(5):2767-2774.
43. Boreddy SR, Srivastava SK. Deguelin suppresses epithelial to mesenchymal transition (EMT) in pancreatic cancer cells by Snail repression and RKIP induction: pivotal role of NF-κB. *Cancer Res*. 2011;71:2-3705.
44. Yu D, Ye T, Xiang Y, et al. Quercetin inhibits epithelial-mesenchymal transition, decreases invasiveness and metastasis, and reverses IL-6 induced epithelial-mesenchymal transition, expression of MMP by inhibiting STAT3 signaling in pancreatic cancer cells. *OncoTargets Ther*. 2017;10:4719-4729.
45. Cao YC, Hu JL, Sui JY, Jiang LM, Cong YK, Ren GQ. Quercetin is able to alleviate TGF-induced fibrosis in renal tubular epithelial cells by suppressing miR-21. *Exp Ther Med*. 2018;16(3):2442-2448.
46. Xing S, Yu W, Zhang X, et al. Isoviolanthin extracted from Dendrobium officinale reverses TGF-β1-mediated epithelial-mesenchymal transition in hepatocellular carcinoma cells via deactivating the TGF-β/Smad and PI3K/Akt/mTOR signaling pathways. *Int J Mol Sci*. 2018;19(6):1556.
47. Chen JL, Chang H, Peng XL, et al. 3,6-Dihydroxyflavone suppresses the epithelial-mesenchymal transition in breast cancer cells by inhibiting the Notch signaling pathway. *Sci Rep*. 2016;6:9.
48. Yang GN, Zhao ZJ, Zhang XX, et al. Effect of berberine on the renal tubular epithelial-to-mesenchymal transition by inhibition of the Notch/snail pathway in diabetic nephropathy model KKAy mice. *Drug Des Devel Ther*. 2017;11:1065-1079.
49. Kou Y, Li L, Li H, et al. Berberine suppressed epithelial mesenchymal transition through cross-talk regulation of PI3K/Akt and RARα/RARβ in melanoma cells. *Biochem Biophys Res Commun*. 2016;479(2):290-296.
50. Du XM, Qi F, Lu SY, Li YC, Han W. Nicotine upregulates FGFR3 and RB1 expression and promotes non-small cell lung cancer cell proliferation and epithelial-to-mesenchymal transition via downregulation of miR-99b and miR-192. *Biomed Pharmacother*. 2018;101:656-662.
51. Liu W, Zhang BL, Chen G, et al. Targeting miR-21 with sophocarpine inhibits tumor progression and reverses epithelial-mesenchymal transition in head and neck cancer. *Mol Ther*. 2017;25(9):2129-2139.
52. Zhang PP, Wang PQ, Qiao CP, et al. Differentiation therapy of hepatocellular carcinoma by inhibiting the activity of Akt/GSK-3β/β-catenin axis and TGF-β induced EMT with sophocarpine. *Cancer Lett*. 2016;376(1):95-103.
53. Wei JL, Li ZR, Yuan F. Evodiamine might inhibit TGF-β1-induced epithelial-mesenchymal transition in NRK52E cells via Smad and PPAR-γ pathway. *Cell Biol Int*. 2014;38(7):875-880.
54. Lu GY, Huang SM, Liu ST, Liu PY, Chou WY, Lin WS. Caffeine induces tumor cytotoxicity via the regulation of alternative splicing in subsets of cancer-associated genes. *Int J Biochem Cell Biol*. 2014;47:83-92.
55. Gordillo-Bastidas D, Oceguera-Contreras E, Salazar-Montes A, Gonzalez-Cuevas J, Hernandez-Ortega LD, Armendariz-Borunda J. Nrf2 and Snail-1 in the prevention of experimental liver fibrosis by caffeine. *Word J Gastroentero*. 2013;19(47):9020-9033.
56. Deng GL, Zeng S, Ma JL, et al. The anti-tumor activities of Neferine on cell invasion and oxaliplatin sensitivity regulated by EMT via Snail signaling in hepatocellular carcinoma. *Sci Rep*. 2017;7:14.
57. Wang YD, Wu ZY, Hu LK. The regulatory effects of metformin on the Snail/miR-34: ZEB/miR-200 system in the epithelial-mesenchymal transition (EMT) for colorectal cancer (CRC). *Eur J Pharmacol*. 834, 2018:45-53.
58. Zhang N, Liu YY, Wang YY, Zhao MY, Tu L, Luo F. Decitabine reverses TGF-β1-induced epithelial-mesenchymal transition in non-small-cell lung cancer by regulating miR-200/ZEB axis. *Drug Des Devel Ther*. 2017;11:969-983.
59. Zhang X, Wang XH, Xu R, et al. YM155 decreases radiation-induced invasion and reverses epithelial-mesenchymal transition by targeting STAT3 in glioblastoma. *J Trans Med*. 2018;16:11.
60. Li LF, Lee CS, Lin CW, et al. Trichostatin A attenuates ventilation-augmented epithelial-mesenchymal transition in mice with bleomycin-induced acute lung injury by suppressing the Akt pathway. *PLOS One*. 2017;12(2):23.
61. Liu S, Gao MW, Wang XQ, et al. Ubenimex attenuates acquired sorafenib resistance in renal cell carcinoma by inhibiting Akt signaling in a lipophagy associated mechanism. *Oncotarget*. 2016;7(48):79127-79139.
62. Herbertz S, Sawyer JS, Stauber AJ, et al. Clinical development of galunisertib (LY2157299 monohydrate), a small molecule inhibitor of transforming growth factor-β signaling pathway. *Drug Des Devel Ther*. 2015;9:4479-4499.

63. Petersen M, Thorikay M, Deckers M, et al. Oral administration of GW788388, an inhibitor of TGF-β type I and II receptor kinases, decreases renal fibrosis. *Kidney Int*. 2008;73(6):705-715.
64. Liu LR, Wang YY, Yan R, et al. Oxymatrine inhibits renal tubular EMT induced by high glucose via upregulation of SnoN and inhibition of TGF-β1/Smad signaling pathway. *PLOS One*. 2016;11(3):12.
65. Su H, Jin X, Zhang X, et al. FH535 increases the radiosensitivity and reverses epithelial-to-mesenchymal transition of radioresistant esophageal cancer cell line KYSE-150R. *J Trans Med*. 2015;13:104.
66. Du R, Sun WJ, Xia L, et al. Hypoxia-induced down-regulation of microRNA-34a promotes EMT by targeting the Notch signaling pathway in tubular epithelial cells. *PLOS One*. 2012;7(2):12.
67. LoConte NK, Razak ARA, Ivy P, et al. A multicenter phase 1 study of γ-secretase inhibitor RO4929097 in combination with capecitabine in refractory solid tumors. *Invest New Drugs*. 2015;33(1):169-176.
68. Yao YF, Li Y, Zeng XF, Ye Z, Li X, Zhang L. Losartan alleviates renal fibrosis and inhibits endothelial-to-mesenchymal transition (EMT) under high-fat diet-induced hyperglycemia. *Front Pharmacol*. 2018;9:12.
69. Xu S, Jiang B, Wang H, Shen CS, Chen H, Zeng L. Curcumin suppresses intestinal fibrosis by inhibition of PPARγ-mediated epithelial-mesenchymal transition. *Evid Based Complement Alternat Med*. 2017;2017:787606-787612.
70. Li W, Jiang ZD, Xiao X, et al. Curcumin inhibits superoxide dismutase-induced epithelial-to-mesenchymal transition via the PI3K/Akt/NF-κB pathway in pancreatic cancer cells. *Int J Oncol*. 2018;52(5):1593-1602.
71. Gallardo M, Ponce-Cusi R, Calaf GM. Curcumin inhibits epithelial-mesenchymal transition and invasion in breast cancer cells by controlling miR-34a expression. *Cancer Res*. 2017;77:2-1478.
72. Deng QF, Sun X, Zhao L, et al. Curcumin reverse cigarette smoke extract-induced human bladder epithelial-mesenchymal transition via suppresses NF-κB signaling in vitro. *Int J Clin Exp Med*. 2016;9(2):5031-5044.
73. Dermani FK, Saidijam M, Amini R, Mahdavinezhad A, Heydari K, Najafi R. Resveratrol inhibits proliferation, invasion, and epithelial-mesenchymal transition by increasing miR-200c expression in HCT-116 colorectal cancer cells. *J Cell Biochem*. 2017;118(6):1547-1555.
74. Xu JH, Liu DY, Niu HL, et al. Resveratrol reverses Doxorubicin resistance by inhibiting epithelial-mesenchymal transition (EMT) through modulating PTEN/Akt signaling pathway in gastric cancer. *J Exp Clin Cancer Res*. 2017;36:14.
75. Zhang YQ, Liu YJ, Mao YF, Dong WW, Zhu XY, Jiang L. Resveratrol ameliorates lipopolysaccharide-induced epithelial mesenchymal transition and pulmonary fibrosis through suppression of oxidative stress and transforming growth factor-β1 signaling. *Clin Nutr*. 2015;34(4):752-760.
76. Choi SY, Piao ZH, Jin L, et al. Piceatannol attenuates renal fibrosis induced by unilateral ureteral obstruction via downregulation of histone deacetylase 4/5 or p38-MAPK signaling. *PLOS One*. 2016;11(11):21.
77. Hong DR, Park MJ, Jang EH, Jung B, Kim NJ, Kim JH. Hispolon as an inhibitor of TGF-β-induced epithelial-mesenchymal transition in human epithelial cancer cells by co-regulation of TGF-β-Snail/Twist axis. *Oncol Lett*. 2017;14(4):4866-4872.
78. Autanski DB, Nagalingam A, Bonner MY, Arbiser JL, Saxena NK, Sharma D. Honokiol inhibits epithelial-mesenchymal transition in breast cancer cells by targeting signal transducer and activator of transcription 3/ZEB1/E-cadherin axis. *Mol Oncol*. 2014;8(3):565-580.
79. Li WD, Wang Q, Su QZ, et al. Honokiol suppresses renal cancer cells' metastasis via dual-blocking epithelial-mesenchymal transition and cancer stem cell properties through modulating miR-141/ZEB2 signaling. *Mol Cell*. 2014;37(5):383-388.
80. Avtanski DB, Nagalingam A, Bonner MY, Arbiser JL, Saxena NK, Sharma D. Honokiol activates LKB1-miR-34a axis and antagonizes the oncogenic actions of leptin in breast cancer. *Oncotarget*. 2015;6(30):29947-29962.
81. Chen L, Chen DQ, Wang M, et al. Role of RAS/Wnt/β-catenin axis activation in the pathogenesis of podocyte injury and tubulo-interstitial nephropathy. *Chem Biol Interact*. 2017;273:56-72.
82. Lou W, Chen Y, Zhu KY, Deng HZ, Wu TH, Wang J. Polyphyllin I overcomes EMT-associated resistance to erlotinib in lung cancer cells via IL-6/STAT3 pathway inhibition. *Biol Pharm Bull*. 2017;40(8):1306-1313.
83. Liu XW, Sun ZT, Deng JK, et al. Polyphyllin I inhibits invasion and epithelial-mesenchymal transition via CIP2A/PP2A/ERK signaling in prostate cancer. *Int J Oncol*. 2018;53(3):1279-1288.
84. Gao YX, Shi LH, Cao Z, et al. Telocinobufagin inhibits the epithelial-mesenchymal transition of breast cancer cells through the phosphoinositide 3-kinase/protein kinase B/extracellular signal-regulated kinase/Snail signaling pathway. *Oncol Lett*. 2018;15(5):7837-7845.
85. Feng LM, Wang XF, Huang QX. Thymoquinone induces cytotoxicity and reprogramming of EMT in gastric cancer cells by targeting PI3K/Akt/mTOR pathway. *J Biosci*. 2017;42(4):547-554.
86. Kou B, Kou QS, Ma B, et al. Thymoquinone inhibits metastatic phenotype and epithelial-mesenchymal transition in renal cell carcinoma by regulating the LKB1/AMPK signaling pathway. *Oncol Rep*. 2018;40(3):1443-1450.
87. Kou B, Liu W, Zhao W, et al. Thymoquinone inhibits epithelial-mesenchymal transition in prostate cancer cells by negatively regulating the TGF-β/Smad2/3 signaling pathway. *Oncol Rep*. 2017;38(6):3592-3598.

88. Li J, Khan MA, Wei C, et al. Thymoquinone inhibits the migration and invasive characteristics of cervical cancer cells SiHa and CaSki in vitro by targeting epithelial to mesenchymal transition associated transcription factors Twist1 and ZEB1. *Molecules*. 2017;22(12):2105.
89. Xu QH, Ma JG, Lei JJ, et al. α-Mangostin suppresses the viability and epithelial-mesenchymal transition of pancreatic cancer cells by downregulating the PI3K/Akt pathway. *BioMed Res Int*. 2014;2014:546353.
90. Mak KK, Wu ATH, Lee WH, et al. Pterostilbene, a bioactive component of blueberries, suppresses the generation of breast cancer stem cells within tumor microenvironment and metastasis via modulating NF-κB/microRNA 448 circuit. *Mol Nutr Food Res*. 2013;57(7):1123-1134.
91. Gu TT, Chen TY, Yang YZ, et al. Pterostilbene alleviates fructose-induced renal fibrosis by suppressing TGF-β1/TGF-β type I receptor/Smads signaling in proximal tubular epithelial cells. *Eur J Pharmacol*. 2018;842:70-78.
92. Feng HT, Lu JJ, Wang YT, Pei LX, Chen XP. Osthole inhibited TGF β-induced epithelial-mesenchymal transition (EMT) by suppressing NF-κB mediated Snail activation in lung cancer A549 cells. *Cell Adh Migr*. 2017;11(5-6):464-475.
93. Wen YC, Lee WJ, Tan P, et al. By inhibiting snail signaling and miR-23a-3p, osthole suppresses the EMT-mediated metastatic ability in prostate cancer. *Oncotarget*. 2015;6(25):21120-21136.
94. Ricca C, Aillon A, Viano M, Bergandi L, Aldieri E, Silvagno F. Vitamin D inhibits the epithelial-mesenchymal transition by a negative feedback regulation of TGF-β activity. *J Steroid Biochem*. 2019;187:97-105.
95. Li R, Dong TT, Hu C, Lu JJ, Dai J, Liu PS. Salinomycin repressed the epithelial-mesenchymal transition of epithelial ovarian cancer cells via downregulating Wnt/β-catenin pathway. *OncoTargets Ther*. 2017;10:1317-1325.
96. Gao RD, Chen RL, Cao Y, et al. Emodin suppresses TGF-β1-induced epithelial-mesenchymal transition in alveolar epithelial cells through Notch signaling pathway. *Toxicol Appl Pharmacol*. 2017;318:1-7.
97. Ma ZQ, Gulia-Nuss M, Zhang X, Brown MR. Effects of the botanical insecticide, toosendanin, on blood digestion and egg production by female *Aedes aegypti* (Diptera: Culicidae): topical application and ingestion. *J Med Entomol*. 2013;50(1):112-121.
98. Wei MG, Sun W, He WM, Ni L, Yang YY. Ferulic acid attenuates TGF-β1-induced renal cellular fibrosis in NRK-52E cells by inhibiting Smad/ILK/Snail pathway. *Evid Based Complement Alternat Med*. 2015;2015:619720.
99. Chilosi M, Calio A, Rossi A, et al. Epithelial to mesenchymal transition-related proteins ZEB1, β-catenin, and β-tubulin-III in idiopathic pulmonary fibrosis. *Modern Pathol*. 2017;30(1):26-38.
100. Xu M, Cao FL, Li NY, Gao X, Su XJ, Jiang XL. Leptin induces epithelial-to-mesenchymal transition via activation of the ERK signaling pathway in lung cancer cells. *Oncol Lett*. 2018;16(4):4782-4788.
101. Hashiguchi Y, Kawano S, Goto Y, et al. Tumor-suppressive roles of Np63-miR-205 axis in epithelial-mesenchymal transition of oral squamous cell carcinoma via targeting ZEB1 and ZEB2. *J Cell Physiol*. 2018;233(10):6565-6577.
102. Muto Y, Suzuki K, Kato T, et al. Heterogeneous expression of zinc-finger E-box-binding homeobox 1 plays a pivotal role in metastasis via regulation of miR-200c in epithelial-mesenchymal transition. *Int J Oncol*. 2016;49(3):1057-1067.
103. Tang WB, Zheng LF, Yan RH, et al. MiR302a-3p may modulate renal epithelial-mesenchymal transition in diabetic kidney disease by targeting ZEB1. *Nephron*. 2018;138(3):231-242.
104. Chen MX, Nie J, Liu Y, et al. Phase Ib/II study of safety and efficacy of low-dose decitabine-primed chemoimmunotherapy in patients with drug-resistant relapsed/refractory alimentary tract cancer. *Int J Cancer*. 2018;143(6):1530-1540.
105. Mateen S, Raina K, Agarwal C, Chan D, Agarwal R. Silibinin synergizes with histone deacetylase and DNA methyltransferase inhibitors in upregulating E-cadherin expression together with inhibition of migration and invasion of human non-small cell lung cancer cells. *J Pharmacol Exp Ther*. 2013;345(2):206-214.
106. Wang B, Liu T, Wu JC, et al. STAT3 aggravates TGF-β1-induced hepatic epithelial-to-mesenchymal transition and migration. *Biomed Pharmacother*. 2018;98:214-221.
107. Lin XL, Liu MH, Liu YB, et al. Transforming growth factor 1 promotes migration and invasion in HepG2 cells: epithelial-to-mesenchymal transition via JAK/STAT3 signaling. *Int J Mol Med*. 2018;41(1):129-136.
108. Xiao J, Gong YN, Chen Y, et al. IL-6 promotes epithelial-to-mesenchymal transition of human peritoneal mesothelial cells possibly through the JAK2/STAT3 signaling pathway. *Am J Physiol Renal Physiol*. 2017;313(2):F310-F318.
109. Zhang CH, Guo FL, Xu GL, Ma J, Shao F. STAT3 cooperates with Twist to mediate epithelial-mesenchymal transition in human hepatocellular carcinoma cells. *Oncol Rep*. 2015;33(4):1872-1882.
110. Xiong H, Hong J, Du W, et al. Roles of STAT3 and ZEB1 proteins in E-cadherin down-regulation and human colorectal cancer epithelial-mesenchymal transition. *J Biol Chem*. 2012;287(8):5819-5832.
111. Liu JS, Zhong Y, Liu GY, et al. Role of STAT3 signaling in control of EMT of tubular epithelial cells during renal fibrosis. *Cell Physiol Biochem*. 2017;42(6):2552-2558.
112. Wang LL, Zhang F, Cui JY, Chen L, Chen YT, Liu BW. CAFs enhance paclitaxel resistance by inducing EMT through the IL-6/JAK2/STAT3 pathway. *Oncol Rep*. 2018;39(5):2081-2090.
113. Nakada S, Kuboki S, Nojima H, et al. Roles of Pin1 as a key molecule for EMT induction by activation of STAT3 and NF-κB in human gallbladder cancer. *Ann Surg Oncol*. 2019;26(3):907-917.

114. Wang T, Lin F, Sun X, et al. HOXB8 enhances the proliferation and metastasis of colorectal cancer cells by promoting EMT via STAT3 activation. *Cancer Cell Int*. 2019;19:3.
115. Han ML, Wang YM, Guo GC, et al. MicroRNA-30d mediated breast cancer invasion, migration, and EMT by targeting KLF11 and activating STAT3 pathway. *J Cell Biochem*. 2018;119(10):8138-8145.
116. Shao QY, Jiang CM, Sun C, et al. Tanshinone IIA mitigates peritoneal fibrosis by inhibiting EMT via regulation of TGF-β/Smad pathway. *Trop J Pharm Res*. 2017;16(12):2857-2864.
117. Chen L, Yang T, Lu DW, et al. Central role of dysregulation of TGF-β/Smad in CKD progression and potential targets of its treatment. *Biomed Pharmacother*. 2018;101:670-681.
118. Troncone E, Marafini I, Stolfi C, Monteleone G. Transforming growth factor-β1/Smad7 in intestinal immunity, inflammation, and cancer. *Front Immunol*. 2018;9:1407.
119. Fransvea E, Angelotti U, Antonaci S, Giannelli G. Blocking transforming growth factor-β up-regulates E-cadherin and reduces migration and invasion of hepatocellular carcinoma cells. *Hepatology*. 2008;47(5):1557-1566.
120. Chiang KC, Yeh CN, Hsu JT, et al. The vitamin D analog, MART-10, represses metastasis potential via downregulation of epithelial-mesenchymal transition in pancreatic cancer cells. *Cancer Lett*. 2014;354(2):235-244.
121. Mann DA, Oakley F, Marek C, Meso M, Millward-Sadler H, Wright M. The NF-κB inhibitor sulfasalazine enhances recovery from CCl_4 induced fibrosis: therapeutic implications. *Hepatology*. 2003;38(4):591A.
122. Al Dhaheri Y, Eid A, Arafat K, et al. *Origanum majorana* extract induces apoptosis and suppresses migration and invasion of MDA-MB-231 human breast cancer cell line through inactivation of the NF-κB pathway. *Eur J Cancer*. 2012;48:S233-S234.
123. Garg B, Giri B, Modi S, et al. NF-κB in tumor stroma modulates cancer growth in mouse models of pancreatic cancer. *Pancreas*. 2016;45(10):1506-1506.
124. Huang CY, Hsieh NT, Li CI, Weng YT, Liu HS, Lee MF. MED28 regulates epithelial-mesenchymal transition through NF-κB in human breast cancer cells. *J Cell Physiol*. 2017;232(6):1337-1345.
125. Lin YC, Lin JC, Hung CM, et al. Osthole inhibits insulin-like growth factor-1-induced epithelial to mesenchymal transition via the inhibition of PI3K/Akt signaling pathway in human brain cancer cells. *J Agr Food Chem*. 2014;62(22):5061-5071.
126. Su CM, Lee WH, Wu ATH, et al. Pterostilbene inhibits triple-negative breast cancer metastasis via inducing microRNA-205 expression and negatively modulates epithelial-to-mesenchymal transition. *J Nutr Biochem*. 2015;26(6):675-685.
127. Zhao YY. Traditional uses, phytochemistry, pharmacology, pharmacokinetics and quality control of *Polyporus umbellatus* (Pers.) Fries: a review. *J Ethnopharmacol*. 2013;149(1):35-48.
128. Zhao YY, Shen X, Chao X, et al. Ergosta-4,6,8(14),22-tetraen-3-one induces G2/M cell cycle arrest and apoptosis in human hepatocellular carcinoma HepG2 cells. *Biochim Biophys Acta Gen Subject*. 2011;1810(4):384-390.
129. Zhao YY, Chao X, Zhang YM, Lin RC, Sun WJ. Cytotoxic steroids from *Polyporus umbellatus*. *Planta Med*. 2010;76(15):1755-1758.
130. Zhao YY, Xie RM, Chao X, Zhang YM, Lin RC, Sun WJ. Bioactivity-directed isolation, identification of diuretic compounds from *Polyporus umbellatus*. *J Ethnopharmacol*. 2009;126(1):184-187.
131. Zhao YY, Cheng XL, Cui JH, et al. Effect of ergosta-4,6,8(14),22-tetraen-3-one (ergone) on adenine-induced chronic renal failure rat: a serum metabonomic study based on ultra performance liquid chromatography/high-sensitivity mass spectrometry coupled with MassLynx i-FIT algorithm. *Clin Chim Acta*. 2012;413(19-20):1438-1445.
132. Zhao YY, Shen XF, Cheng XL, Wei F, Bai X, Lin RC. Urinary metabonomics study on the protective effects of ergosta-4,6,8(14),22-tetraen-3-one on chronic renal failure in rats using UPLC Q-TOF/MS and a novel MS^E data collection technique. *Process Biochem*. 2012;47(12):1980-1987.
133. Zhao YY, Chen H, Tian T, Chen DQ, Bai X, Wei F. A pharmaco-metabonomic study on chronic kidney disease and therapeutic effect of ergone by UPLC-QTOF/HDMS. *PLOS One*. 2014;9(12):e115467.
134. Zhao YY, Zhang L, Long FY, et al. UPLC-Q-TOF/HSMS/MS^E-based metabonomics for adenine-induced changes in metabolic profiles of rat faeces and intervention effects of ergosta-4,6,8(14),22-tetraen-3-one. *Chem Biol Interact*. 2013;201(1-3):31-38.
135. Zhao YY, Zhang L, Mao JR, et al. Ergosta-4,6,8(14),22-tetraen-3-one isolated from *Polyporus umbellatu*s prevents early renal injury in aristolochic acid-induced nephropathy rats. *J Pharm Pharmacol*. 2011;63(12):1581-1586.
136. Chen H, Cao G, Chen DQ, et al. Metabolomics insights into activated redox signaling and lipid metabolism dysfunction in chronic kidney disease progression. *Redox Biol*. 2016;10:168-178.
137. Chen L, Chen DQ, Liu JR, et al. Unilateral ureteral obstruction causes gut microbial dysbiosis and metabolome disorders contributing to tubulointerstitial fibrosis. *Exp Mol Med*. 2019;51(3):38.
138. Zhang J, Cai HQ, Sun LX, et al. LGR5, a novel functional glioma stem cell marker, promotes EMT by activating the Wnt/β-catenin pathway and predicts poor survival of glioma patients. *J Exp Clin Cancer Res*. 2018;37:16.
139. Xie SL, Fan S, Zhang SY, et al. SOX8 regulates cancer stem-like properties and cisplatin-induced EMT in tongue squamous cell carcinoma by acting on the Wnt/β-catenin pathway. *Int J Cancer*. 2018;142(6):1252-1265.

140. Zhang E, Yang Y, Chen S, et al. Bone marrow mesenchymal stromal cells attenuate silica-induced pulmonary fibrosis potentially by attenuating Wnt/β-catenin signaling in rats. *Stem Cell Res Ther*. 2018;9(1):311.
141. Chen DQ, Cao G, Chen H, et al. Gene and protein expressions and metabolomics exhibit activated redox signaling and Wnt/β-catenin pathway are associated with metabolite dysfunction in patients with chronic kidney disease. *Redox Biol*. 2017;12:505-521.
142. Krishnamurthy N, Kurzrock R. Targeting the Wnt/β-catenin pathway in cancer: update on effectors and inhibitors. *Cancer Treat Rev*. 2018;62:50-60.
143. Tu XZ, Hong D, Jiang YY, et al. FH535 inhibits proliferation and migration of colorectal cancer cells by regulating CyclinA2 and Claudin1 gene expression. *Gene*. 2019;690:48-56.
144. Liu X, Du P, Han L, Zhang AL, Jiang K, Zhang QY. Effects of miR-200a and FH535 combined with taxol on proliferation and invasion of gastric cancer. *Pathol Res Pract*. 2018;214(3):442-449.
145. Turcios L, Vilchez V, Acosta LF, et al. Sorafenib and FH535 in combination act synergistically on hepatocellular carcinoma by targeting cell bioenergetics and mitochondrial function. *Dig Liver Dis*. 2017;49(6):697-704.
146. Xia GS, Li SH, Zhou W. Isoquercitrin, ingredients in Tetrastigma hemsleyanum Diels et Gilg, inhibits hepatocyte growth factor/scatter factor-induced tumor cell migration and invasion. *Cell Adhes Migr*. 2018;12(5):464-471.
147. Liu L, Wang QF, Mao J, et al. Salinomycin suppresses cancer cell sternness and attenuates TGF-β-induced epithelial-mesenchymal transition of renal cell carcinoma cells. *Chem Biol Interact*. 2018;296:145-153.
148. Yu Z, Cheng H, Zhu H, et al. Salinomycin enhances doxorubicin sensitivity through reversing the epithelial-mesenchymal transition of cholangiocarcinoma cells by regulating ARK5. *Brazilian J Med Biol Res*. 2017;50(10):7.
149. Wang YZ, Zhang J, Zhao YL, et al. Mycology, cultivation, traditional uses, phytochemistry and pharmacology of *Wolfiporia cocos* (Schwein.) Ryvarden et Gilb: a review. *J Ethnopharmacol*. 2013;147(2):265-276.
150. Chen DQ, Cao G, Chen H, et al. Identification of serum metabolites associating with chronic kidney disease progression and anti-fibrotic effect of 5-methoxytryptophan. *Nat Commun*. 2019;10(1):1476.
151. Miao H, Zhao YH, Vaziri ND, et al. Lipidomics biomarkers of diet-induced hyperlipidemia and Its treatment with *Poria cocos*. *J Agric Food Chem*. 2016;64(4):969-979.
152. Chen H, Chen L, Tang DD, et al. Metabolomics reveals hyperlipidemic biomarkers and antihyperlipidemic effect of *Poria cocos*. *Curr Metabolomics*. 2016;4(2):104-115.
153. Miao H, Li MH, Zhang X, Yuan SJ, Ho CC, Zhao YY. The antihyperlipidemic effect of Fu-Ling-Pi is associated with abnormal fatty acid metabolism as assessed by UPLC-HDMS-based lipidomics. *RSC Adv*. 2015;5(79):64208-64219.
154. Zhao YY, Feng YL, Du X, Xi ZH, Cheng XL, Wei F. Diuretic activity of the ethanol and aqueous extracts of the surface layer of *Poria cocos* in rat. *J Ethnopharmacol*. 2012;144(3):775-778.
155. Feng YL, Lei P, Tian T, et al. Diuretic activity of some fractions of the epidermis of *Poria cocos*. *J Ethnopharmacol*. 2013;150(3):1114-1118.
156. Zhao YY, Feng YL, Bai X, Tan XJ, Lin RC, Mei Q. Ultra performance liquid chromatography-based metabonomic study of therapeutic effect of the surface layer of *Poria cocos* on adenine-induced chronic kidney disease provides new insight into anti-fibrosis mechanism. *PLOS One*. 2013;8(3):e59617.
157. Zhao YY, Li HT, Feng YI, Bai X, Lin RC. Urinary metabonomic study of the surface layer of *Poria cocos* as an effective treatment for chronic renal injury in rats. *J Ethnopharmacol*. 2013;148(2):403-410.
158. Zhao YY, Lei P, Chen DQ, Feng YL, Bai X. Renal metabolic profiling of early renal injury and renoprotective effects of *Poria cocos* epidermis using UPLC Q-TOF/HSMS/MS^E. *J Pharm Biomed Anal*. 2013;81-82:202-209.
159. Wang M, Chen DQ, Wang MC, et al. Poricoic acid ZA, a novel RAS inhibitor, attenuates tubulo-interstitial fibrosis and podocyte injury by inhibiting TGF-β/Smad signaling pathway. *Phytomedicine*. 2017;36:243-253.
160. Chen L, Cao G, Wang M, et al. The matrix metalloproteinase-13 Inhibitor poricoic acid ZI ameliorates renal fibrosis by mitigating epithelial-mesenchymal transition. *Mol Nutr Food Res*. 2019;63(12):e1900132.
161. Chen DQ, Feng YL, Chen L, et al. Poricoic acid A enhances melatonin inhibition of AKI-to-CKD transition by regulating Gas6/Axl-NF-κB/Nrf2 axis. *Free Radic Biol Med*. 2019;134:484-497.
162. Wang M, Chen DQ, Chen L, et al. Novel RAS inhibitors poricoic acid ZG and poricoic acid ZH attenuate renal fibrosis via a Wnt/β-catenin pathway and targeted phosphorylation of Smad3 signaling. *J Agr Food Chem*. 2018;66(8):1828-1842.
163. Tian T, Chen H, Zhao YY. Traditional uses, phytochemistry, pharmacology, toxicology and quality control of *Alisma orientale* (Sam.) Juzep: a review. *J Ethnopharmacol*. 2014;158:373-387.
164. Feng YL, Chen H, Tian T, Chen DQ, Zhao YY, Lin RC. Diuretic and anti-diuretic activities of the ethanol and aqueous extracts of *Alismatis rhizoma*. *J Ethnopharmacol*. 2014;154(2):386-390.
165. Chen DQ, Feng YL, Tian T, et al. Diuretic and anti-diuretic activities of fractions of Alismatis rhizoma. *J Ethnopharmacol*. 2014;157:114-118.
166. Miao H, Zhang L, Chen DQ, Chen H, Zhao YY, Ma SC. Urinary biomarker and treatment mechanism of *Rhizoma Alismatis* on hyperlipidemia. *Biomed Chromatogr*. 2017;31(4):e3829.

167. Dou F, Miao H, Wang JW, et al. An integrated lipidomics and phenotype study reveals protective effect and biochemical mechanism of traditionally used *Alisma orientale* Juzepzuk in chronic kidney disease. *Front Pharmacol*. 2018;9:53.
168. Wang FQ, Ruan LT, Yang JR, Zhao QL, Wei W. TRIM14 promotes the migration and invasion of gastric cancer by regulating epithelial-to-mesenchymal transition via activation of Akt signaling regulated by miR-195-5p. *Oncol Rep*. 2018;40(6):3273-3284.
169. Feng YJ, Hu X, Liu GW, et al. M3 muscarinic acetylcholine receptors regulate epithelial-mesenchymal transition, perineural invasion, and migration/metastasis in cholangiocarcinoma through the Akt pathway. *Cancer Cell Int*. 2018;18:12.
170. Dou Y, Lei JQ, Guo SL, Zhao D, Yue HM, Yu Q. The CNPY2 enhances epithelial-mesenchymal transition via activating the Akt/GSK3 pathway in non-small cell lung cancer. *Cell Biol Int*. 2018;42(8):959-964.
171. Jiang B, Guan Y, Shen HJ, et al. Akt/PKB signaling regulates cigarette smoke-induced pulmonary epithelial-mesenchymal transition. *Lung Cancer*. 2018;122:44-53.
172. Pan T, Chen WJ, Yuan XM, Shen J, Qin C, Wang LB. MiR-944 inhibits metastasis of gastric cancer by preventing the epithelial-mesenchymal transition via MACC1/Met/Akt signaling. *FEBS Open Bio*. 2017;7(7):905-914.
173. Xu QR, Liu X, Liu ZK, et al. MicroRNA-1296 inhibits metastasis and epithelial-mesenchymal transition of hepatocellular carcinoma by targeting SRPK1-mediated PI3K/Akt pathway. *Mol Cancer*. 2017;16:15.
174. Lin D, Kuang G, Wan JY, et al. Luteolin suppresses the metastasis of triple-negative breast cancer by reversing epithelial-to-mesenchymal transition via downregulation of β-catenin expression. *Oncol Rep*. 2017;37(2):895-902.
175. Spencer M, Finlin BS, Unal R, et al. Omega-3 fatty acids reduce adipose tissue macrophages in human subjects with insulin resistance. *Diabetes*. 2013;62(5):1709-1717.
176. Yuan L, Lang TY, Jin BW, et al. Luteolin inhibits colorectal cancer cell epithelial-to-mesenchymal transition by suppressing CREB1 expression revealed by comparative proteomics study. *J Proteomics*. 2017;161:1-10.
177. Yan XL, Wang YY, Yu ZF, Tian MM, Li H. Peroxisome proliferator-activated receptor-γactivation attenuates diabetic cardiomyopathy via regulation of the TGF-β/ERK pathway and epithelial-to-mesenchymal transition. *Life Sci*. 2018;213:269-278.
178. Sheng XD, Chen H, Wang H, et al. MicroRNA-130b promotes cell migration and invasion by targeting peroxisome proliferator-activated receptor γ in human glioma. *Biomed Pharmacother*. 2015;76:121-126.
179. Hatanaka H, Koizumi N, Okumura N, et al. Epithelial-mesenchymal transition-like phenotypic changes of retinal pigment epithelium induced by TGF-β are prevented by PPAR-γ agonists. *Invest Ophthalmol Vis Sci*. 2012;53(11):6955-6963.
180. Lv J, Sun BH, Mai ZT, Jiang MM, Du JF. CLDN-1 promoted the epithelial to migration and mesenchymal transition (EMT) in human bronchial epithelial cells via Notch pathway. *Mol Cell Biochem*. 2017;432(1-2):91-98.
181. Zhang LH, Sha JJ, Yang GL, Huang XY, Bo JJ, Huang YR. Activation of Notch pathway is linked with epithelial-mesenchymal transition in prostate cancer cells. *Cell Cycle*. 2017;16(10):999-1007.
182. Zhou JS, Jain S, Azad A, et al. Notch and TGF β form a positive regulatory loop and regulate EMT in epithelial ovarian cancer cells. *Cell Signal*. 2016;28(8):838-849.
183. Zhang JP, Zheng GJ, Zhou L, et al. Notch signalling induces epithelial-mesenchymal transition to promote metastasis in oral squamous cell carcinoma. *Int J Mol Med*. 2018;42(4):2276-2284.
184. Yuan X, Wu H, Han N, et al. Notch signaling and EMT in non-small cell lung cancer: biological significance and therapeutic application. *J Hematol Oncol*. 2014;7:87.
185. Pan E, Supko JG, Kaley TJ, et al. Phase I study of RO4929097 with bevacizumab in patients with recurrent malignant glioma. *J Neurooncol*. 2016;130(3):571-579.
186. Diaz-Padilla I, Hirte H, Oza AM, et al. A phase Ib combination study of RO4929097, a γ-secretase inhibitor, and temsirolimus in patients with advanced solid tumors. *Invest New Drugs*. 2013;31(5):1182-1191.
187. Okamoto K, Tajima H, Nakanuma S, et al. Angiotensin II enhances epithelial-to-mesenchymal transition through the interaction between activated hepatic stellate cells and the stromal cell-derived factor-1/CXCR4 axis in intrahepatic cholangiocarcinoma. *Int J Oncol*. 2012;41(2):573-582.
188. Gong QY, Hou FL. Silencing of angiotensin II type-1 receptor inhibits high glucose-induced epithelial-mesenchymal transition in human renal proximal tubular epithelial cells via inactivation of mTOR/p70S6K signaling pathway. *Biochem Biophys Res Commun*. 2016;469(2):183-188.
189. Oh E, Kim JY, Cho Y, et al. Overexpression of angiotensin II type 1 receptor in breast cancer cells induces epithelial-mesenchymal transition and promotes tumor growth and angiogenesis. *Biochim Biophys Acta, Mol Cell Res*. 2016;1863(6):1071-1081.
190. Pinter M, Kwanten WJ, Jain RK. Renin-angiotensin system inhibitors to mitigate cancer treatment-related adverse events. *Clin Cancer Res*. 2018;24(16):3803-3812.

191. Martin N, Manoharan K, Thomas J, Davies C, Lumbers RT. β-Blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. *Cochrane Database Syst Rev*. 2018; 6:199.
192. Lu F, Ye Y, Zhang H, et al. MiR-497/Wnt3a/c-jun feedback loop regulates growth and epithelial-to-mesenchymal transition phenotype in glioma cells. *Int J Biol Macromol*. 2018;120:985-991.
193. Lu J, Lin YX, Li FY, et al. MiR-205 suppresses tumor growth, invasion, and epithelial-mesenchymal transition by targeting SEMA4C in hepatocellular carcinoma. *FASEB J*. 2018;32(11):6123-6134.
194. Yan H, Sun BM, Zhang YY, et al. Upregulation of miR-183-5p is responsible for the promotion of apoptosis and inhibition of the epithelial-mesenchymal transition, proliferation, invasion and migration of human endometrial cancer cells by downregulating Ezrin. *Int J Mol Med*. 2018;42(5):2469-2480.
195. Yin Q, Han Y, Zhu DY, et al. MiR-145 and miR-497 suppress TGF-β-induced epithelial-mesenchymal transition of non-small cell lung cancer by targeting MTDH. *Cancer Cell Int*. 2018;18:9.
196. Li JF, Wang QR, Wen RL, et al. MiR-138 inhibits cell proliferation and reverses epithelial-mesenchymal transition in non-small cell lung cancer cells by targeting GIT1 and SEMA4C. *J Cell Mol Med*. 2015;19(12):2793-2805.
197. Guo RS, Hao GJ, Bao Y, et al. MiR-200a negatively regulates TGF-β1-induced epithelial-mesenchymal transition of peritoneal mesothelial cells by targeting ZEB1/2 expression. *Am J Physiol Renal Physiol*. 2018;314(6):F1087-F1095.
198. Yang X, Hu Q, Hu LX, et al. MiR-200b regulates epithelial-mesenchymal transition of chemo-resistant breast cancer cells by targeting FN1. *Discov Med*. 2017;24(131):75-85.
199. Lv ZD, Kong B, Liu XP, et al. MiR-655 suppresses epithelial-to-mesenchymal transition by targeting Prrx1 in triple-negative breast cancer. *J Cell Mol Med*. 2016;20(5):864-873.
200. Cao JM, Li GZ, Han M, Xu HL, Huang KM. MiR-30c-5p suppresses migration, invasion and epithelial to mesenchymal transition of gastric cancer via targeting MTA1. *Biomed Pharmacother*. 2017;93:554-560.
201. Li L, Wu DP. MiR-32 inhibits proliferation, epithelial-mesenchymal transition, and metastasis by targeting TWIST1 in non-small-cell lung cancer cells. *OncoTargets Ther*. 2016;9:1489-1498.
202. Stinson S, Lackner MR, Adai AT, et al. MiR-221/222 targeting of trichorhinophalangeal 1 (TRPS1) promotes epithelial-to-mesenchymal transition in breast cancer. *Sci Signal*. 2011;4(186):4-pt5.
203. Liu MN, Liu LM, Bai M, et al. Hypoxia-induced activation of Twist/miR-214/E-cadherin axis promotes renal tubular epithelial cell mesenchymal transition and renal fibrosis. *Biochem Biophys Res Commun*. 2018;495(3):2324-2330.
204. Zhiping C, Shijun T, Linhui W, Yapei W, Lianxi Q, Qiang D. MiR-181a promotes epithelial to mesenchymal transition of prostate cancer cells by targeting TGIF2. *Eur Rev Med Pharmacol*. 2017;21(21):4835-4843.
205. Chen KJ, Li Q, Weng CM, et al. Bleomycin-enhanced alternative splicing of fibroblast growth factor receptor 2 induces epithelial to mesenchymal transition in lung fibrosis. *Biosci Rep*. 2018;38(6):BSR20180445.
206. Jeong HM, Han J, Lee SH, et al. ESRP1 is overexpressed in ovarian cancer and promotes switching from mesenchymal to epithelial phenotype in ovarian cancer cells. *Oncogenesis*. 2017;6:13.
207. Braeutigam C, Rago L, Rolke A, Waldmeier L, Christofori G, Winter J. The RNA-binding protein Rbfox2: an essential regulator of EMT-driven alternative splicing and a mediator of cellular invasion. *Oncogene*. 2014;33(9):1082-1092.
208. Zhang G, Isaji T, Xu Z, Lu X, Fukuda T, Gu J. N-acetylglucosaminyltransferase-I as a novel regulator of epithelial-mesenchymal transition. *FASEB J*. 2018;33(2):2823-2835.
209. Xu QS, Isaji T, Lu YY, et al. Roles of N-acetylglucosaminyltransferase III in epithelial-to-mesenchymal transition induced by transforming growth factor β1 (TGF-β1) in epithelial cell lines. *J Biol Chem*. 2012;287(20):16563-16574.
210. Avasarala S, Van Scoyk M, Rathinam MKK, et al. PRMT1 is a novel regulator of epithelial-mesenchymal-transition in non-small cell lung cancer. *J Biol Chem*. 2015;290(21):13479-13489.
211. Monteiro FL, Vitorino R, Wang J, et al. The histone H2A isoform Hist2h2ac is a novel regulator of proliferation and epithelial-mesenchymal transition in mammary epithelial and in breast cancer cells. *Cancer Lett*. 2017;396:42-52.
212. Xia HP, Chen JX, Shi M, et al. EDIL3 is a novel regulator of epithelial-mesenchymal transition controlling early recurrence of hepatocellular carcinoma. *J Hepatol*. 2015;63(4):863-873.
213. Zhang R, Wei YH, Zhao CY, et al. EDIL3 depletion suppress epithelial-mesenchymal transition of lens epithelial cells via transforming growth factor β pathway. *Int J Ophthalmol*. 2018;11(1):18-24.
214. Gao ZH, Lu C, Wang ZN, et al. ILEI: a novel marker for epithelial-mesenchymal transition and poor prognosis in colorectal cancer. *Histopathology*. 2014;65(4):527-538.
215. Zhu BQ, Zhang Q, Wang JR, Mei XF. Cocrystals of baicalein with higher solubility and enhanced bioavailability. *Cryst Growth Des*. 2017;17(4):1893-1901.
216. Yin JT, Xiang CY, Wang PQ, Yin YY, Hou YT. Biocompatible nanoemulsions based on hemp oil and less surfactants for oral delivery of baicalein with enhanced bioavailability. *Int J Nanomed*. 2017;12:2923-2931.
217. Zhou Y, Dong WJ, Ye J, et al. A novel matrix dispersion based on phospholipid complex for improving oral bioavailability of baicalein: preparation, in vitro and in vivo evaluations. *Drug Deliv*. 2017;24(1):720-728.

AUTHOR BIOGRAPHIES

Ya-Long Feng received his BS degree in Northwest University, China, in 2012. After completing his undergraduate studies, he joined the research group of Prof Ying-Yong Zhao. He started his PhD at 2014 and concentrates on natural products against tissue fibrosis.

Dan-Qian Chen received her BS degree at Northwest University, China, in 2015. Since 2012, she was admitted into the Key Laboratory of Resource Biology and Biotechnology in Western China and joined the research group of Prof Ying-Yong Zhao. She started her PhD at 2015 and focuses on the fibrogenesis mechanism and natural products against fibrosis.

Nosratola D. Vaziri obtained his PhD in 1966 from Tehran University. He is currently working as a researcher at Division of Nephrology and Hypertension, School of Medicine, University of California Irvine. His current research focuses on oxidative stress, inflammation, microbial dysbiosis, NO metabolism and mechanisms of lipid disorders in chronic renal disease and proteinuria.

Yan Guo obtainted his PhD in 2009 from University of South Carolina. He is currently an associate professor at the Department of Internal Medicine, University of New Mexico. His current research focuses on bioinformatics and therapeutic effect of natural products against tissue fibrosis.

Ying-Yong Zhao was awarded his PhD in 2010 from Northwest University. He is currently pharmacology professor at School of Pharmacy, Faculty of Life Science and Medicine, Northwest University in China. He has recognized contributions in natural product chemistry, renal pharmacology, and system biology. He serves as Scientific Reports, American Journal of Nephrology, and Current Metabolomics of the editorial board as well as Frontiers in Medicine Associate Editor and Pharmacognosy Magazine Editor. Zhao has authored 120 peer-reviewed publications in Trends in Pharmacological Sciences, British Journal of Pharmacology, Redox Biology, Nephrology Dialysis Transplantation, Experimental and Molecular Medicine and Phytomedicine. These publications were cited more than 4500 times in the past 5 years. He received several awards including National Excellent Doctoral Dissertation Nomination Award, New Century Excellent Talents in University, Sanofi Young biological drugs Award and Fifteenth SERVIER Youth Pharmacology Award. His study mainly focuses on the mechanism of chronic kidney disease and therapeutic effect by using natural products.

How to cite this article: Feng YL, Chen DQ, Vaziri ND, Guo Y, Zhao YY. Small molecule inhibitors of epithelial-mesenchymal transition for the treatment of cancer and fibrosis. *Med Res Rev*. 2019;1-25. https://doi.org/10.1002/med.21596